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Original Communications

MALIGNANT CARCINOID OF THE SMALL INTESTINE WITH METASTASES TO THE LIVER, VALVULAR DISEASE OF THE RIGHT SIDE OF THE HEART (PULMONARY STENOSIS AND TRICUSPID REGURGITATION WITHOUT SEPTAL DEFECTS), PERIPHERAL VASOMOTOR SYMPTOMS, BRONCHOCONSTRICTION, AND AN UNUSUAL TYPE OF CYANOSIS

A CLINICAL AND PATHOLOGIC SYNDROME

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IN 1951, a young man (Case 1) with vasomotor symptoms of a peculiar type (rapidly changing cyanotic patches) and symptoms of valvular disease of the right side of the heart was admitted to the Medical Department, The General Hospital, Malmö. The patient died after an angiocardiographic examination, and the autopsy revealed pulmonary stenosis, tricuspid regurgitation, and a small carcinoid of the ileum with extensive abdominal metastases. In the report[1] of the case, no satisfactory explanation of the vasomotor disturbance could be given. In an addendum, Cases 2 and 3 were briefly mentioned.

During the spring of 1952, a woman with the same type of discoloration of the skin was observed by one of us (J. W.) and Dr. E. Ljungberg at the Medical Department, The Central Hospital, Ängelholm, Sweden (Chief: Dr. E. Ljungberg). The symptoms had been in progress for 10 years. She had no symptoms of any heart disease, but in 1944 she had had a malignant carcinoid of the ileum excised. At the time of operation there was already widespread metastases (Case 3).

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In June, 1952, an old man from the General Hospital, Malmö, (Case 2) at autopsy was shown to have pulmonary stenosis, tricuspid insufficiency, and a malignant carcinoid of the distal ileum with large metastases to lymph nodes and liver (Dr. G. Björkman).

These three case histories were read, and Case 2 was demonstrated at a meeting in Malmö, June, 1952. The similarities of the symptoms and findings in the patients seemingly indicated a close relationship between the lesions in the intestine, the skin, and the heart, and one of us (J. W.) suggested that attention to such skin lesions would bring forth more cases. This was stressed in a paper by Waldenström and Ljungberg.[2] (The lesions will be mentioned later in this paper and will also be detailed in a paper by Waldenström and Ljungberg[3] now in press.)

In September, 1952, another woman (Case 4) with the characteristic changing, patchy distribution, reddenings and cyanotic areas was observed by Dr. O. Nordenfelt (Senior Physician, the Medical Department, The Central Hospital, Jönköping), who, then, suspected a carcinoid of the small intestine. This was confirmed at operation and later by the microscopic examination. The patient in January, 1953, was referred to the Medical Department, Malmö, for study.

Still another diagnosis of intestinal carcinoid according to these skin lesions was made by Dr. O. Ljung (Senior Physician, The Central Hospital of Karlstad, Sweden) in December, 1952. It was reported by him[4] and will be referred to later. Unfortunately the patient died following an explorative laparotomy, and there was only a partial autopsy. The liver showed carcinoid metastases.

In January, 1953, Isler and Hedinger[5] from the Kantonenspital in Zürich reported three cases of carcinoids of the small intestine with extensive metastases to abdominal organs and "chronic endocarditis," most pronounced in the right side of the heart and producing pulmonary stenosis and tricuspid insufficiency (Cases 7, 8, and 9). They had at the time of their report no knowledge of the Swedish cases. The Swiss authors described the autopsy findings and microscopic examinations and also gave concentrated case histories. Severe cyanosis was mentioned in all three patients. They also referred to a case reported by Scholte[6] and expressed their belief that carcinoids of the ileum with metastases to the liver, pulmonary stenosis, and tricuspid insufficiency constitute a definite syndrome.

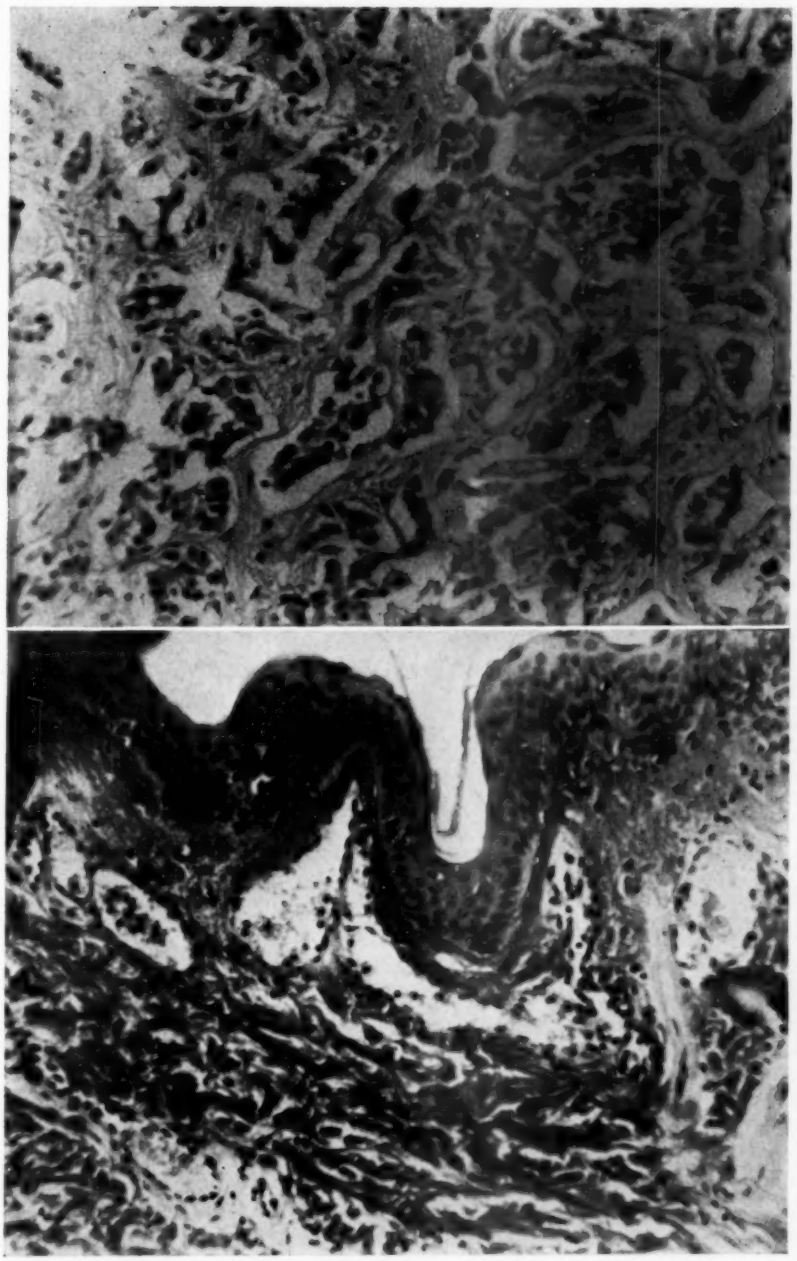
Rosenbaum and associates, in October 1953, reported two cases, one of which definitely and the other one with great probability belong to this syndrome (Cases 15 and 16). Only an abstract of their report has as yet been published.[7]

In this paper, we will describe the cases mentioned in some detail together with another case from our hospital records and four more cases from earlier literature that showed many similarities with others in this series. We believe that discoloration of the skin is an essential symptom, in many instances enabling the diagnosis of carcinoids. The persistent cyanosis described and the valvular disease are seemingly late manifestations.

CASE REPORTS

CASE 1.—This case has already been reported.[1] K.G. was a 19-year-old boy, who had no history of rheumatic fever. From the age of six, dyspnea on exertion was observed. In the years

A.



B.

Fig. 1.—*A*, Microscopic slide from intestinal tumor (K.G.). For particulars see the text. *B*, Slide from abdominal skin (K.G.). Shows widening of the vessels.

1943, 1945, and 1946, he was hospitalized with a diagnosis of bronchial asthma, the chief features of which, however, were cyanosis, "exanthema" over the face and body, and sudden dyspnea. Sibilant ronchi were heard over the lungs. Auscultation over the heart and roentgenographic studies did not indicate any cardiac disease at that time. He had had for several years color changes in the skin similar to those reported in the patient S.H.; they were observed by the family doctor.[8]

In 1951, liver enlargement, pitting edema and systolic and diastolic murmurs over the heart were observed. Blood pressure readings varied considerably: one week 140/105 mm. Hg was recorded; one week later, only 105/65 mm. Hg. From about this time there was a regression of the attacks of dyspnea but the general course was downhill. He complained of frequent spasmodic pain in the abdomen and had diarrhea periodically. He was referred to our hospital in 1951.

We found a weak, underdeveloped boy with physical findings indicating a combined valvular disease, probably in the right side of the heart. There was pitting edema and moderate ascites. The liver was considerably enlarged, soft and nontender with pronounced systolic pulsations and a systolic murmur.

The dorsal regions of the forearms showed a brownish, scaly thickening of the skin, which had appeared after exposure to sunshine. There was a curious color of the skin, the constituents of which were changing patches of blue, deep red, and a bright brick red. A more detailed recording of this and other findings was given in the earlier case report.[1]

The electrocardiogram showed a right bundle branch block.

On cardiac catheterization, high pressures were recorded in both venae cavae and in the right atrium. A violent regurgitant flow prevented access to the right ventricle.

Angiocardiography showed pulmonary valvular stenosis. At the termination of anesthesia the patient developed ventricular fibrillation and died.

The autopsy (Dr. S. Winblad) revealed a moderate valvular pulmonary stenosis due to partial fusion of the pulmonary cusps. These showed fibrosis at the margins but no sign of acute inflammation. The tricuspid orifice was very wide and the cusps were thickened and showed fibrosis and an acute infiltration with round cells. The right ventricle and atrium were enlarged with muscular hypertrophy.

In the middle of the small intestine there was a small tumor with one single glandular metastasis and extensive metastases to the large liver.

The tumor of the small intestine and the metastases were composed of strands and irregular solid masses of spheroidal and polygonal cells with defined cytoplasmic borders and darkstaining round or oval nuclei. Glandular formations were also seen. The tumor masses were supported by a scant amount of collagen stroma. The microscopic picture was that of a carcinoid (Fig. 1, *A*).

Slides from the skin showed an extreme dilatation of all capillaries and postcapillary veins (Fig. 1, *B*).

CASE 2.—S.M. was a 63-year-old man. He had previously been in good health. From 1916 to 1936, he suffered from recurrent attacks of sub-ileus with abdominal distention and pain immediately after meals and alternating constipation and diarrhea. In 1936, a stricture of the lower ileum was found and an ileoileostomy which completely relieved his symptoms was performed. At the operation there was found a tumorous infiltration, big as a hen's egg, in the mesentery corresponding to the site of the firm white intestinal stricture. For technical reasons the tumor and stricture could not be extirpated. From 1943, he had periodically frequent loose stools, which gradually increased to continuous diarrhea with as much as 10 to 25 small watery stools every day in 1951 and 1952. He also had periods of sharp pain in the lower back and abdomen and intermittent fever. Repeated roentgenograms of the stomach and intestinal tract only showed quick passage in the small intestine and diverticulosis and, at times, irritation of the sigmoid colon. In 1936, roentgenograms showed slight widening of the left ventricle and marked widening of the thoracic aorta. The Wassermann test was negative.

From 1943, he got dyspneic on exertion and after meals when he also had "heat waves" with reddening of the sclera. He also had attacks of nocturnal dyspnea with wheezing respiration and cough, which was relieved by Adrenalin. During his last two years these attacks ceased but the dyspnea increased, the liver was enlarged, and he had edema of the legs. From 1949 to 1952, he was hospitalized repeatedly. The second aortic sound on these occasions was exaggerated. The sounds were otherwise normal. No murmurs were heard. Blood pressure readings ranged between

220/140 and 150/100 mm. Hg. During his last months, he developed a constant hypotension. Venous pressure readings ranged between 4.5 and 20 cm. of water. Electrocardiograms only showed left-axis deviation. The edema was treated with digitalis without much benefit, but sodium restriction, rest, and mercurial diuretics gave temporary relief.

In the records from 1936, he had been noted to be pale. During later years he had a plethoric color and polycythemia was suspected in 1949 and 1950, when he actually was anemic with red blood count 3.4 and 3.6 millions and 64 and 65 per cent hemoglobin, respectively. The blood values returned to normal on iron therapy, only to decrease to the former values, and later could not be restored by iron intravenously or liver compounds. No blood was found in the stools. The total plasma protein was 6.5 to 5.9 gram per cent. In 1952, he became gradually weaker and lost weight rapidly; the anemia increased, the liver surface was found to be uneven, and there was a palpable tumor behind the lower end of his old laparotomy scar. He expired on June 6, 1952.

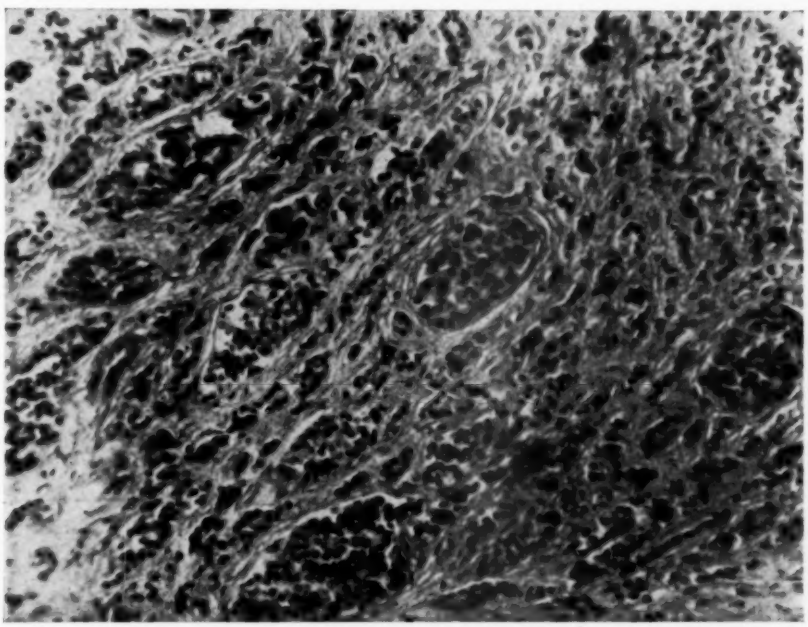


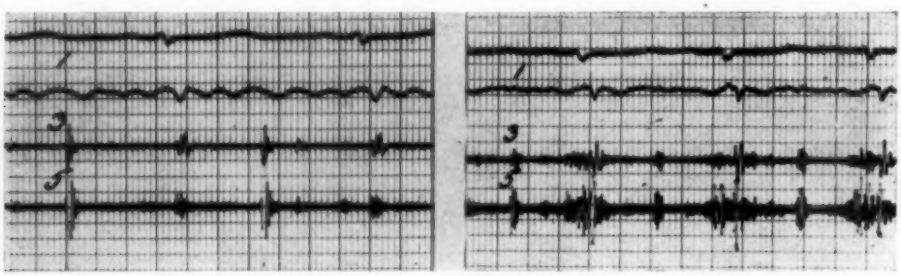
Fig. 2.—Microscopic slide from the intestinal tumor (S.M.). For particulars see the text.

The autopsy (Dr. G. Björkman) showed: narrowing of the pulmonary ostium and sclerosis and some retraction of the pulmonary cusps creating a stenosis of the pulmonary orifice, which only admitted the introduction of the second finger. There was partial fusion of the cusps at the marginal insertion. The aortic valve was dilated with separation of the cusps. Two of the aortic cusps were broad but otherwise normal, the third only rudimentary. There was no syphilitic aortitis, and the aorta did not appear widened. The mitral and tricuspid valves were normal. The epi- and endocardial surfaces were normal. There was moderate muscular hypertrophy of both ventricular walls; the heart weighed 380 grams. The coronary arteries were wide and tortuous. They showed no atheromatosis, and there was no infarction of the heart. In the left pleural sac 200 c.c. clear yellow serous effusion was found. The lungs were emphysematous with basal bronchopneumonic infiltrations. In the distal coil of the ileum which was shunted off by the ileostomy, 20 cm. from the ileocecal valve was found a firm constricting tumor which projected as a polyp into the lumen. There also was found a solitary metastasis, big as a hen's egg in the mesentery. This status seems to have been unchanged since the operation in 1936. There were extensive metastases to the para-aortic nodes, the omentum, the head and tail of the pancreas and the liver. The metastases were in part necrotic and hemorrhagic. Slides from the tumor and the metastases showed pictures (Fig. 2) identical with those from Case 1.

The following three cases show no apparent signs of valvular heart disease but with this exception have the typical findings of this series. They have been included because of their excellent demonstration of the typical signs in the peripheral circulation. Case 3 has previously been reported with comments.[2] Further studies will be reported later.[3,9]

CASE 3.—E.P. is a 43-year-old woman. During adolescence she was repeatedly treated for tonsillitis and polyposis nasi until tonsillectomy was performed in 1927. She was also treated for dysmenorrhea and menorrhagia. The uterus was found myomatous and the ovaries were enlarged in 1943.

From 1940, she suffered from sudden flushes. During the first years they were initiated by anxiety or muscular effort, later also by strong spices and hot food. However, they often came on seemingly spontaneously. They were accompanied by an extreme feeling of heat, tachycardia, and weakness and were sometimes followed by dizziness and prostration. The flushes are of the same type as in Case 4. They will be detailed under the heading Cutaneous Phenomena.



A. *B.*

Fig. 3.—Phonocardiograms from the apex region (E.P.). *A*, Before, and *B*, a few minutes later during a moderate flush. Corresponding tracings were taken with the same channels and the same amplification. Note the appearance during flush of a presystolic and systolic murmur and also the change in loudness of the heart sounds.

From 1947 to 1950, she showed wheezing and stridorous expiration at the termination of the major flushes and was told that she had "asthma." This gradually diminished. From 1942, she could feel a small resistance to the left in her abdomen. She was operated on for this in May, 1944. There was found a constricting tumor of the small intestine with metastases in the regional lymph node, the ovaries, and the liver. The tumor was excised and at the microscopic examination was shown to be a carcinoid. (Prof. A. Lindau.)

From 1943, she has had diarrhea: one to two, at most five, watery stools a day, decreasing in the latter years. She has frequent borborygmi and severe abdominal pain.

There has been no edema or ascites. During the last six months she has become very weak, and lost appetite and weight. During recent years, she has been studied several times at hospitals. The heart studies have always been normal, also during flushing. She has recently been studied at the Medical Department, Malmö.

She was very weak and thin and she looks very ill during days with repeated flushing (there can be as many as 24 flushes a day).

The heart sounds were found normal in flush-free intervals. During early flushing there now appears a Grade 3 systolic murmur over the second and third left intercostal spaces. Phonocardiograms show it to begin in late presystole (Fig. 3). The second pulmonic sound is normal. Electrocardiograms including right-sided chest leads and unipolar limb leads are normal and do not change during flush. Ballistocardiographic studies will be reported in a separate paper together with studies of pulse, heart rate, and systolic and diastolic arterial blood pressure.[9] The peripheral arteries are very prominent and pulsate vigorously during flush. There are no venous pulsations and the veins are not distended. There is no clubbing.

There is sometimes expiratory stridor during regression of the flush. The liver is enlarged and slightly tender. Roentgenograms of the small intestine only show quickened passage. Some

of the most pertinent laboratory findings are: red blood count, 4.0 million with 80 per cent hemoglobin. Sedimentation rate 3 mm. in one hour.

CASE 4.—This is the case of Nordenfelt in which a diagnosis of intestinal carcinoid was suspected owing to the peculiar type of "flush" and cyanosis described by Waldenström and Ljungberg. S.H., a 48-year-old woman, in 1941 suffered from cholelithiasis, and a cholecystectomy was done with relief of symptoms. That year she also was hospitalized for acute polyarthritis. Since then she has had no arthritic symptoms.

In 1942, she began to blush, or rather, "flush." She became rapidly and intensely red all over the body and felt uncomfortably warm. She also felt pain in her abdomen after meals. Since 1948, the pain has been more sudden and sharp in the epigastrium. There were borborygmi and she developed diarrhea, from 8 to 10, even 20, sudden watery stools a day. She saw no blood in the stools. There was a connection between the borborygmi and the flushing of her skin. From 1950, she observed patchy cyanosis which came at the termination of the flush and gave her skin a "geographical" pattern as "red islands in a blue sea." She also observed permanently wide blue veins on her nose and cheeks. Both flush and cyanosis varied in intensity from hour to hour and day to day but showed slow progress until October, 1952. The flushes often were initiated by intake of food and followed by slight dizziness during the cyanotic stage. She also had slight ankle edema in the evening. She was hospitalized in Jönköping, Sweden, in September, 1952. A malignant carcinoid was suspected by Dr. Nordenfelt. Roentgenograms showed an intestinal tumor with dilatation of the jejunum but rapid passage.

She was operated in October, 1952, when there was found a yellow-white tumor of the small intestine with metastases retroperitoneally, in the omentum, both ovaries, and the liver which was enlarged. There was brownish-yellow ascites. The intestinal tumor was excised together with the right ovary and the retroperitoneal and omental metastases.

Immediately after operation, her flushes diminished in frequency as did the borborygmi and diarrhea, her appetite improved and she put on weight. She no longer has spells of dizziness and she feels better than for several years. The ankle edema has, however, increased, which partially explains her gain in weight. She is slightly anemic. She was admitted to our hospital in February, 1953, for study. Some of these studies are reported later in this paper. Other studies are mentioned in a paper by Waldenström and Ljungberg[3] now in press.*

The microscopic examination showed the excised tumors to be a carcinoid with metastases.

CASE 5.—This is the case diagnosed and reported by O. Ljung.[4] B.G., a 43-year-old man, had an appendectomy in 1946 after an acute incidence of abdominal symptoms. The appendix was macroscopically normal. From about that time he had recurrent periods of abdominal discomfort. He was examined by physicians in 1950, 1951, and 1952. In 1952, a big bulging epigastrial tumor was found, which previously had not been palpated.

During 1951, the patient had episodes of ankle edema. The edema increased during 1952, but there was no dyspnea. The patient had "always" had a high facial color. During 1950, this rapidly increased and deepened, and he showed marked changing between vivid redness, normal color, and blanching of the face. These changes could occur several times a day. No predisposing factors were observed. From 1952, the color was a permanent extreme redness.

He was hospitalized on Feb. 16, 1953 (County Hospital, Karlstad). At the time of observation in the hospital the reddening was confined to his face. It was slightly cyanotic and much more intense than in any case of polycythemia or alcoholism observed by the physicians of the hospital. There was no clubbing. The eyegrounds were normal. There was marked edema in the legs. A slight systolic murmur was heard over the entire precordium. The arterial blood pressure was 150/100 mm. Hg; the venous pressure, 12 cm. saline. An electrocardiogram was normal. Roentgenograms showed normal lung fields and slight enlargement of the heart. A big rounded tumor bulged the upper abdomen. Roentgenograms of the stomach, large bowel, kidneys, and gall bladder showed impressions and dislocations due to the tumor.

Laboratory findings revealed a negative Meinicke test, hemoglobin 70 per cent, and red blood count 3.4 million. White blood count and differential count were normal, as was the bone marrow. Platelets 100,000. Total serum protein was 6.2 per cent. Takata test negative; thymol extinction

*In 1953, there were no indications of any heart disease. In April, 1954, a strong, harsh, systolic murmur had developed. See also footnote page 815.

test 0.4 unit. Alkaline phosphatases, 5.2 units. Nonprotein nitrogen, 33 mg. per cent. The urine showed traces of albumen but no sugar.

After the communication of Waldenström and Ljungberg about skin lesions in carcinoids the tumor was believed by Ljung to be caused by carcinoid metastases in the liver, but an exploratory laparotomy was made as the tumor appeared to be cystic.

At the operation on March 2, the liver was riddled with big yellow-white tumors. A biopsy showed the characteristics of carcinoid metastases in the liver (Prof. R. Fåhreus).

The day after the operation the patient had fever, the nonprotein nitrogen increased, and he expired on March 9.

Only a partial autopsy was performed (not by a pathologist). No primary tumor was found and no metastasis in any organ except the liver was observed. The heart was found enlarged. Owing to unfortunate circumstances, no satisfactory organ autopsy and no microscopic examinations were made.

In his article the author[4] expressed the opinion that the combination of vascular phenomenona of the type reported and carcinoids already seems to be an established fact and not only a coincidence.

In our hospital records we found the history of E. K.

CASE 6.—E.K., a 59-year-old woman, had felt weak and nervous since 1924. In 1938, she was hospitalized for disagreeable hot flushes. She was thought to be neurotic. Her heart status was then regarded to be normal. Since about that time she suffered from severe flushes. During the first six to seven years, they came on suddenly with intense reddening of the face and neck, and she felt hot and uncomfortable all over the skin. Between the flushes, which especially were initiated by food, her face had normal color. From about 1945, the color got deeper red with a cyanotic tinge, and a butterfly area over the nose and cheeks became distinctly cyanotic during flushes. Between flushes, it later became permanently red and during her last months permanently deep blue. The rest of her face became permanently red and coarse. The temporal arteries often pulsated vigorously for a while and she felt so dizzy that she had to lie down. If she then tried to sit up she got intensely cyanotic and fell back. She felt very weak but was remarkably stimulated by strong coffee.

From 1945, she had 3 to 5 loose stools every day and in addition frequent tenesmus, often initiated by meals. Roentgenographic examinations of the large intestine and stomach were normal.

She developed hyposalivation and xerostomia. Later she became weaker, had diffuse pain in the abdomen and intermittent attacks of sharp pain in the lower abdomen and lost weight.

From 1950, she had intermittent edema of the legs. This became permanent and increased in 1950 with swelling of the abdomen. She was thought to suffer from heart failure by two visiting physicians. Digitalis was tried without benefit.

The patient was referred to the medical department on April 2, 1950. She was then extremely ill and cachectic with dyspnea and marked edema of the legs. Her skin was dry and atrophic, most markedly on her hands and feet but also all over the body. She had deep cyanosis of the face, especially over the nose and cheeks. Her forearms, hands and legs also were cyanotic, and visible mucous membranes were markedly red with a cyanotic tinge.

There was a weak systolic murmur over the upper precordium, especially over the pulmonic area. The blood pressure was 165/125 mm. Hg. The liver was enlarged and reached below the umbilicus. Its surface was uneven with ascites.

Laboratory findings: Hemoglobin, 90 per cent; red blood count, 4.2 million. Sedimentation rate 30 mm. in one hour. An electrocardiogram showed right-axis deviation with high-peaked P waves and diphasic T waves in Leads II, III and CR_4.

The attending physician was puzzled over the deep cyanosis, which he could not explain. The day after admission she developed Cheyne-Stokes respiration and expired.

The autopsy revealed multiple small tumors in the lower ileum 2 cm. above the ileocecal valve with glandular metastases in the mesentery root. Other groups of lymph nodes belonging to the prevertebral pelvic regions also showed metastatic infiltration, as did both the ovaries.

The liver showed numerous small metastases. The tumors of intestine, lymph nodes, liver, and ovaries showed the same microscopic picture. They were composed of cords and trabeculae made up of rather large, uniform cells with pale cytoplasm and round nuclei with delicate chromatin granules and large distinct nucleoli. Only very few mitoses were seen. The tumor masses were supported by slender strands of collagen stroma. The microscopic picture was that of a carcinoid (Fig. 4).

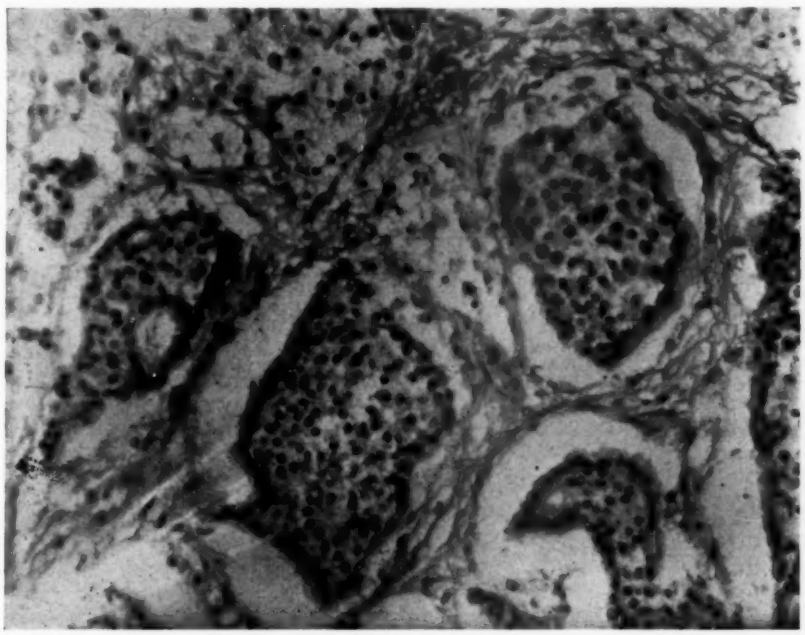


Fig. 4.—Microscopic slide from the intestinal tumor (E.K.). For particulars see the text.

At the post-mortem examination, the heart was noted to be normal. Clinically there were no auscultatory signs indicating a valvular disease. The electrocardiographic findings, however, suggest strain of the right side of the heart and are strikingly similar to most electrocardiograms from patients with well-developed pulmonary stenosis.[10] There were no clinical signs, and there were no autopsy findings except slight emphysema indicating a pulmonary genesis. Both exaggerated P waves and right-axis deviation may be caused by a vertical position of the heart, but we do not think that this is the sole cause in this patient with such marked changes.

We are more inclined to regard this finding as indicating an increased pulmonary vascular resistance, either functional or organic in nature. If functional, it might be regarded as an earlier phase in a development of structural valvular disease. If organic, it might easily have been overlooked at autopsy owing to the current technique of opening the heart, as pointed out by Green and associates,[11] the lesions in some of the cases of this series not being very pronounced.

Isler and Hedinger[5] have published three cases from Zürich that showed carcinoids of the small intestine, disseminated metastases, pulmonary stenosis, tricuspid regurgitation, and marked cyanosis. We summarize their report here.

CASE 7.—A 56-year-old woman had formerly been in good health. Some months before her death she developed diarrhea with 6 to 8 watery stools a day, abdominal pain, and cachexia. Later there was marked edema of the abdomen and legs with reddened skin and pruritus. At the time of hospitalization she had marked edema and deep cyanosis despite a hemoglobin of only 82 per cent. The skin was bluish red and scaling. The heart sounds were strong with loud systolic murmurs over all orifices. The pulse was very thin with blood pressure 120/80 mm. Hg. A roentgenogram of the heart was normal. An electrocardiogram showed rather high P waves in Leads I and II. The abdomen protruded and was tender, the liver enlarged. Laboratory findings were also suggestive of liver disease. Repeated roentgenographic examinations of the stomach and the intestinal tract were negative. Digitalization was tried but resulted in vomiting. She deteriorated rapidly and died three weeks after admittance.

The autopsy showed dilatation of the right atrium and both ventricles with muscular hypertrophy of the right heart. There was scarring and vascularization of the tricuspid leaflets. The pulmonary valves were thickened and fused, creating a stenosis of the ostium. The circumference of the tricuspid ostium was 6 cm., the pulmonic 4.5 cm., the mitral 9 cm. and the aortic 6.5 cm. Cholelithiasis and cholecystitis were found. There was a small intestinal tumor 1 M. from the flexura duodenojejunalis. The liver was enlarged and studded with metastases, large as cherries. There was metastatic infiltration also in the right ovary. The tumor and the metastases showed the morphology of an intestinal carcinoid. (Particulars of the autopsy are given in the original paper.)[4]

CASE 8.—A 64-year-old woman was hospitalized because of progressing dyspnea, cyanosis, and edema for one year and enlargement of the liver for several months. She also had 6 to 8 watery stools a day. On admission she was in a poor nutritional state and showed marked cyanosis, dyspnea, and peripheral edema of the legs, where the skin was atrophic, reddened, and pruriginous.

The heart sounds were loud with exaggeration of the second pulmonic sound and a harsh systolic murmur all over the heart, a short diastolic murmur, and a protodiastolic gallop rhythm. An electrocardiogram showed right-axis deviation. The abdomen protruded and was tender. The liver was enlarged with uneven margin.

Laboratory findings suggested impaired function of the liver. The hemoglobin was 85 per cent and the peripheral blood normal. Repeated roentgenograms of the stomach and the passage time were normal.

Digitalization caused profuse vomiting. Her symptoms progressed and she died 11 months after the first admittance.

At autopsy there were found dilatation and hypertrophy of the right ventricle and dilatation of the right atrium. The pulmonary cusps were fused and thickened and the circumference was only 5 cm. The tricuspid valve also showed fusion and thickening, the circumference was 9 cm., and the chordae tendineae were shortened and thickened. The valves showed vascularization but no infiltration.

In the distal part of the ileum there were eight small tumors; one of these could be followed into the mesentery.

The liver was studded with metastases and there were also metastases in the right ovary. The tumor and the metastases were microscopically shown to be of carcinoid nature.

CASE 9.—A 33-year-old man, had shown intermittent cyanosis since his fourteenth year and had been told that he had heart disease.

When he was hospitalized he had progressive cyanosis and pain in the left half of the chest. He showed intense cyanosis and slight ankle edema. The liver was large, tender, and pulsating. The veins of the neck also pulsated. There were systolic murmurs over all orifices. The second heart sound was clearly audible over the entire precordium and was after a short pause followed at the apex and in the pulmonary area by a weak diastolic murmur. The heart was enlarged to the left and the electrocardiogram showed right bundle branch block. In the first left rib there was a tumor, which was found to be radiosensitive. A biopsy of the tumor showed the characteristics of a solid carcinoma. There was slow progression of the edema, cyanosis, liver enlargement, and enlargement of the heart. Digitalization was without effect and the patient died.

The autopsy showed a carcinoid tumor of the ileum, 120 cm. proximal to the ileocecal valve, with stenosis of the lumen and solitary metastases in the mesentery and at the porta hepatis. The liver was studded with metastases and there was also a small tumorous infiltration in the left kidney.

The microscopic appearance of the metastases was somewhat varied and showed in parts columnar cells in bands, and in parts a pure carcinoid. The heart showed right ventricular hypertrophy. The tricuspid valves were sclerosed and retracted. The endocardium of the right atrium was patchily thickened. The circumferences of the ostia were: the tricuspid, 8 cm.; the pulmonary, 3.5 cm.; the mitral, 9 cm.; and the aortic, 6 cm. The microscopic examination showed vascularization and sclerosis of the valves. The thickened patches of the endocardium of the right atrium were constituted by dense collagen. There was no inflammatory infiltration.

Isler and Hedinger believed their three cases to be members of the same syndrome and cite also that of Scholte.[6] They do not mention any opinion regarding the pathogenesis.

CASE 10.—In 1931, the findings in a 47-year-old man were reported.[4] From childhood he had a remarkable bluish red color to his face. The color grew deeper in the last three years before his death, and the skin of his legs and body also got more red. He was admitted to the dermatologic ward where by microscopic examination a great number of thin-walled pools of blood in the corium were found. These vessels gave rise to the peculiar color. A diagnosis of capillary ectases or angiomatous new growth was made. At this hospitalization there was also found an enlargement of the heart by percussion and a systolic murmur over the pulmonary orifice. No edema is mentioned on this occasion. In 1928, he was hospitalized in the medical department of the University in Amsterdam. His complaints then were dyspnea, cyanosis, and watery stools (the duration of these latter symptoms was not mentioned). The liver was enlarged and firm. The physical findings seem to have been unchanged. In February 1929, he was again admitted because of signs of heart failure and confusion, watery stools, and loss of weight. He died 3 weeks later.

At autopsy there was found some hyaline degeneration and general widening with stasis in the precapillary arteries, the capillaries, and the postcapillary veins in the superficial layers of the corium and to a lesser degree in the subcutaneous tissues.

The heart showed pulmonary stenosis with thickened and shortened cusps holding a fine capillary network and abundant fibroblasts. There was also lymphocytic infiltration. The tricuspid leaflets showed marked sclerosis. The endocardium of the right atrium showed thickened patches. There was marked hypertrophy and dilatation of the right ventricle.

The lungs showed bronchopneumonia and a small infarction with a pleural exudate.

A flat intestinal tumor 1 by 1 cm. was found 50 cm. before the ileocecal valve. At the corresponding site in the mesentery there was a big glandular metastasis which caused some obstruction to the lumen.

The liver was studded with metastases. There were also a number of concretions in the gall bladder. The parenchymatous organs showed congestion. The tumors were found by microscopic examination to be a carcinoid with metastases.

Scholte in his report did not believe in passive congestion as the cause of the vascular changes, but would not venture any definite opinion as to the cause. He believed that the patient suffered from three different maladies: (1) angiomatosis, (2) chronic endocarditis, and (3) a malignant carcinoid of the ileum.

Among the eleven cases of pulmonary stenosis reported by Currens and associates[12] we believe there is one patient who belongs to this syndrome (their Case 4). The findings are only briefly summarized here:

CASE 11.—The patient was a 43-year-old actress, who from childhood had had much indigestion with intermittent episodes of upper abdominal pain.

On admittance she complained of progressive weakness, diarrhea with 4 to 6 small watery stools a day, weight loss, ankle edema, frequent night sweats, a sore mouth, cutaneous hyperesthesia, and circumscribed areas over the dorsum of each hand, where the skin showed a dusky red discoloration with a good deal of crustation. These symptoms had lasted about 10 months. She had had some loss of memory and mental confusion for an indefinite period. There had been no history of dyspnea, cyanosis, or "heart disease."

At examination she had generalized anasarca. The face was edematous, and the skin and lips were moderately cyanotic. The tongue was red and raw. The heart sounds were of good quality, the second pulmonic sound equal to the second aortic sound. There was a loud systolic murmur, and also a short rough diastolic murmur, best heard in the second and third intercostal spaces to the left of the sternum. (The pulse rate varied from 90 to 120.)

The abdomen was distended and a large irregular mass was palpable in the region of the liver. The laboratory findings were: red blood count, 5 million; white blood count, 12,000 to 18,000; normal differential count; urine, normal; total serum protein, 6.1 gram per cent.

A roentgenogram revealed a slight prominence of the pulmonary conus. An electrocardiogram showed slight depression of S-T_1, flat T_1 and T_2 and a low T_3.

Full digitalization was without benefit, as was a diet rich in vitamins. There was rapid progression of the symptoms and she died after three weeks.

The autopsy diagnosis was (1) carcinoma of the ileum with metastases to the liver, ovaries, and thoracic duct, (2) pellagra, (3) pulmonary stenosis, (4) chronic passive congestion of the liver, and (5) ascites.

The right ventricular wall showed muscular hypertrophy. The pulmonary orifice measured 4.5 cm. in circumference and was moderately stenotic. The valve edges were thicker and more fibrous than normal. The surface of the valves was smooth. The mitral, tricuspid, and aortic valves were normal.

No microscopic examination of the tumor and the metastases was reported. According to the great similarity of symptoms and findings in this case and in the others reported in this series it may be permissible to suppose the tumor to be a carcinoid rather than a carcinoma, which is also rare in the ileum.

Arnett and Long[13] in 1931 described a case which seems to have many points in common with our patients.

CASE 12.—This patient was a muscular 32-year-old man, who did not remember any previous illness. Several thorough examinations had revealed nothing abnormal with his heart.

In 1927, he had an attack of cyanosis when chilled and afterwards these attacks got more frequent. He also had two attacks of severe dyspnea.

In February, 1929, he developed ankle edema and a remarkable bluish-purple tinge and was hospitalized in April, 1929. The color was then deepest in the face, where it was a splotchy purple. This color was mainly or entirely due to the presence of engorged, deeply purple superficial blood vessels, many of which were visible to the naked eye. Microscopic examination of the finger by the Lombard method showed more numerous and more tortuous capillaries than are usually found. Portions of the trunk and the extremities also presented a purplish appearance. On striking the skin of the finger there was left a blanched trail for a few seconds. This quickly gave way to a bluish discoloration, and this in turn to a brick red color with blanched margins, the latter phenomenon lasting about 5 minutes. There was absence of cyanosis of the lips and fingernail beds. The response of the skin of the forearm to needle pricks through solutions of Adrenalin and also of histamine was normal. Physical examination revealed a very harsh systolic murmur over the entire precordium. It was best heard at the third intercostal space to the left of the sternum. There was no clubbing of the fingers. The arterial blood pressure was recorded to be 102/68 mm. Hg. Roentgenographic examination showed slight increase of the left ventricular image and of that of the right auricle. An electrocardiogram showed right-axis deviation. No venous pulsations were visible and the veins of the hand were seen to collapse when the hand was raised to the level of the chin. The eyegrounds were reported normal. The liver was felt 3 cm. below the margin and was hard. The white blood count was 10,000. Other hematologic findings were normal. The urine showed traces of albumin. The fasting blood sugar was 50 mg. per cent. At a glucose tolerance test the blood sugar rose to 260 mg. per cent after 2 hours with 1.1 Gm. per cent of sugar in the urine.

The edema disappeared on rest and digitalis therapy, only to reappear rapidly. In May, diarrhea appeared, which persisted unto his death with 8 to 10 watery stools every day. He lost weight and got very weak, had curious seizures of shortness of breath, choking cough and at times cerebral attacks, when he was irrational during the night but rational in the day. The liver

became more enlarged. The skin of the legs was tense and shiny. Finally he got aphasic, had exaggerated pateller reflexes, Babinski's sign, and myoclonic twitchings. He died in November, 1929.

At autopsy the right half of the heart seemed dilated. The epicardium was found normal. There was a moderate pulmonary stenosis. The sizes of the orifices were as follows: mitral, 8.5 cm.; tricuspid, 9 cm.; aortic, 6.4 cm.; and pulmonic, 3.5 cm. The wall of the left ventricle was 14 mm. thick and that of the right ventricle 6 mm. There was a small foramen ovale which was thought to be functionally closed, but no other septal defects. The heart muscle showed hypertrophy and edema. The pancreas measured 12 by 4 by 3 cm., was of a yellowish color and firm consistency and contained several nodules. The microscopic examination is reported to have revealed an adenocarcinoma of the pancreas. The liver was studded with metastases, and there were metastastic infiltrations in the lymph nodes around the cystic duct and retroperitoneally. No other metastases were found. The authors believed that in the agsence of any signs of infection, the pulmonary stenosis must be of congenital origin, although they found his previous good conditions and the absence of symptoms at earlier examinations most remarkable.

Microscopic slides of the skin showed numerous blood vessels with dilated and thickened walls. The authors attributed the patchy cyanosis to local dilatations of superficial vessels with stasis of blood and supposed some connection between the heart disease and this dilatation.

This unusually sturdy patient also showed a bluish-red discoloration with transient attacks of irregularly distributed cyanotic spots (before there were observed any auscultatory symptoms of pulmonary stenosis), severe diarrhea, pellagra-like lesions, and cerebral seizures which might have been induced by vasomotoric alterations. The anatomic diagnosis was carcinoma of the pancreas, but the history (notably the absence of pain or jaundice) is rather atypical for this diagnosis. Moreover the pancreas often shows metastases in malignant carcinoids (as in two of our own cases) of the intestine, and primary carcinoid growth has been shown by Feyrter[14] to occur in pancreatic remnants. We believe that this case shows so many features in common with our other cases that we include it in this series, as it is an example of a patient with curious vasomotoric symptoms, malignant disease of the digestive tract, and a moderate stenosis of the pulmonary valve.

Sir Maurice Cassidy has reported two cases of malignant abdominal disease with hepatic engagement and during a long time repeated flushings of the face. In one of these a well-marked valvular pulmonary stenosis was found at autopsy. In all probability it belongs to this syndrome.[15,16]

CASE 13.—A.W., a man, aged 31, knew of no previous serious illness. In June 1926, he complained of "rushes of blood to the face." In May, 1928, he was ill for two days with pain across the sacrum followed for several weeks by loose motions. He improved in June, 1928, and remained well for two years. During the summer of 1930, he suffered from recurrent attacks of diarrhea, flushing of the face, and to a less extent of the body, attacks of palpitation and dyspnea, several attacks of frequent micturition. There was persistent cough but roentgenograms of the lungs were normal. The bowel movements were irregular, periods of normal actions for a week or more alternating with attacks of watery diarrhea with movements as often as every half hour, day and night. During these attacks there was often frequent painless micturition. He was admitted to St. Thomas's Hospital, Sept. 18, 1930. On admission there was noted: phenomenal flushing of face, much exaggerated during emotion or during a meal, and numerous dilated venules of recent origin over the nose and cheeks. The skin of the trunk was usually of a mottled mauve color but with sudden changes to a vermillion hue. An exceptionally brilliant tache appeared slowly, lasted for a few minutes, and left a pallid zone of cutaneous vasoconstriction behind. Examination of the heart revealed a loud blowing systolic murmur down the left sternal margin, best heard near the fourth left intercostal space. This was felt to get louder and harsher during a

few weeks of observation. Arterial blood pressure, 150/120 mm. Hg. Pulse rate, 90 to 100. Temperature, subnormal. In his abdomen the liver was found enlarged, hard and irregular and the right kidney was enlarged. A hard large mass filled the pelvis partially constricting the rectum two inches above the anus.

Among the laboratory tests may be mentioned: Löwi's Adrenalin pupillary reaction, negative; a moderate normochromic anemia; white blood count, 12,000 with a normal differential count; blood urea, 75 mg. per 100 c.c.; a low specific gravity of urine but no abnormal constituents. An electrocardiogram showed flat T waves.

There was very slow progression of symptoms. He developed recurrent ascites and hard edema of the legs eventually and died on Feb. 5, 1931.

At the post-mortem the lungs showed edema of the lower lobes. The heart weighed 270 grams and showed a well-marked stenosis of the pulmonary valve. The pulmonary artery above the valve was of normal dimensions. The ductus arteriosus was closed and the intracardiac septa uninterrupted.

The abdomen contained a large amount of slightly purulent fluid. The stomach was smaller than normal with a normal mucous membrane. The large bowel appeared somewhat contracted. There was no dilation of the small intestine. (No mention of any organ autopsy of the small intestine was made in the report.)

The liver was greatly enlarged and contained a large number of white, on the serosal surface often umbilicated, nodules.

The pelvic organs were embedded in a very firm and large mass causing partial constriction of the hollow structures. The urinary bladder was extremely small with a pale mucous membrane. It looked as though the pelvis had been filled with plaster of Paris. There was no evidence of a primary new growth in the rectum, urinary structures, or the adrenals.

The microscopic examination of several different segments of the pelvic "growth" only showed excessive fibrous tissue formation but no malignant tissue at all. Sections from the nodules in the liver showed that these ". . . resembled secondary deposits of columnar carcinoma, dissimilar to secondary deposits arising from a primary carcinoma of the intestine, but consistent with a primary carcinoma of the prostate."

This case shows most of the characteristics of the syndrome. There was nothing abnormal from abdomen or heart noted at several prior examinations, a slow progress of symptoms consisting of flushes, with cyanotic tinge and later telangiectases over the nose and cheeks (according to the excellent color plate published[15]) attacks of palpitations, dyspnea and diarrhea for several years. Rapidly progressing auscultatory findings indicated valvular disease (no murmurs were noted in 1928, the blood pressure was then 140/80 mm. Hg), ascites, and edema of the legs.

The post mortem showed a malignant abdominal condition with extensive involvement of the liver and a pure valvular pulmonary stenosis. The microscopic appearance of the liver nodules was confusing.[15,16] Cassidy also reported a 48-year-old man, F. K., with malignant disease of the digestive tract, extensive metastases to the liver, typical sudden and rapidly changing flushes of the skin and marked variations in systolic and diastolic arterial blood pressure.[17] Whether this case belongs to this syndrome is a matter of dispute as the tumor was reported to be a carcinoma of the stomach and there were no physical findings indicating any valvular lesions, but it is referred to here for comparison.

CASE 14.—F.K. had "always" had a high color. From 1931, he experienced slowly increasing attacks of intense flushing of the head, trunk, and legs, often accompanied by palpitations and with a definite relationship to meals, beginning during eating. Sometimes defecation induced an attack. He had no diarrhea, but a good deal of flatulence with belching. He had nausea in the mornings. He lost weight. From 1933 he had edema of the legs. On admission to St. Thomas's

Hospital in September 1933, he was thin and wasted with protruding abdomen. His face was very flushed with multiple dilated venules and telangiectasis, arms rather red below elbows, marked erythema palmare, and ankle edema.

There were no abnormal physical findings in the heart or arteries but marked variability of blood pressure, the lowest pressures (112/70 and 125/82 mm. Hg) recorded during flushes. There were ascites and a large irregular mass, which was thought to be the enlarged liver. Red blood count was 5.6 millions; hemoglobin, 95 per cent; no occult blood was found in the stools, but a test meal showed occult blood and absence of free HCl. The course was progressive with wasting and increasing edema and ascites, but the attacks of flushing became less frequent. The patient expired on Dec. 10, 1933.

The autopsy was briefly reported to have shown carcinoma of the stomach with multiple metastases in the liver. The adrenals were normal.

CASES 15 AND 16.—Rosenbaum and associates described the following two cases.[7] We have only recently had access to their published abstract which, of course, gives no very detailed description.

The first patient had for 20 years shown progressive dilatation of the superficial vessels of the skin on the face, later extending to the thorax, abdomen, and upper extremities, and ultimately becoming so severe that the face took on ". . . a frightening, purple gray hue." Histologic studies of the skin disclosed greatly dilated capillaries, venules, and veins considered to be pre-existing rather than newly formed. Venous pressure recordings made from the patient did not indicate pressures of sufficient magnitude to produce this type of dilatation of the vessels. For the last ten years of life (and incidentally from ten to twenty years after the appearance of the "telangiectases") hepatomegaly was found. The later years of life were characterized by progressive ". . . congestive heart failure, primarily right ventricular in origin."

Post-mortem examination disclosed severe pulmonic and tricuspid stenosis with minor mitral valvular involvement and a carcinoid of the ileum with extensive hepatic metastases.

The second patient showed the same type of vascular skin lesions for ten years before his death. During his last two years his liver was enlarged and he too showed symptoms of progressive congestive heart failure of the right side. The symptoms and course resembled those of their first case so closely that the clinical diagnosis was reached ante mortem.

The autopsy diagnosis was: severe pulmonic and tricuspid stenosis and extensive adenocarcinoma of the hepatic bile ducts.

In both cases the vascular phenomena were believed by Rosenbaum and his colleagues to have preceded the hepatic disease by several years. No satisfactory explanation of the telangiectases could be given. They were attributed to an alleged rheumatic disease which also would have produced the unusual valvular disturbance. In one of the cases, Aschoff bodies were found (not mentioned in which case). Neither a history of any clinical symptoms of such a rheumatic incident was given, nor any particulars as to clinical symptoms and microscopic autopsy findings.

SUMMARY OF CASE REPORTS

In view of the rarity of both pulmonary stenosis and malignant carcinoid of the small intestine we believe that the fact that several cases have been reported to suffer from both conditions simultaneously makes this rather unsuspected combination a clinical and pathologic syndrome and not a pure coincidence. This conception was reflected by the addendum to the report of our Case 1. One of us (J. W.) and Ljungberg pointed out the peculiar type of flush and cyanosis and showed this in a patient with proved carcinoid and liver metastases. They originally attributed the vasomotor symptoms to the carcinoid and suggested and later emphasized the importance of the cutaneous symptoms as diagnostic signs of carcinoids of the small intestine and also mentioned the possibility of pulmonary stenosis in these cases.[2,3] As already mentioned Isler and Hedinger also suggested that heart lesions of the right side and intestinal carcinoids with metastases to the liver constituted a new syndrome.

TABLE I

Case No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Initials	K.G.	S.M.	E.P.	S.H.	B.G.	E.K.	Z I	Z II	Z III	Sch.	Cur	A – L	C I	C II	R I	R II
Sex	M	M	F	F	M	F	F	F	M	M	M	M	M	M	–	–
Age at death	19	63	43*	48*	43	59	56	64	33	47	43	32	31	48	–	–
Intestinal carcinoid	+	+	+	+	+	+	+	+	+	+	?	?	?	?	+	0
Liver metastases	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ovarial metastases	0	0	+	+	0	+	+	+	0	0	0	0	0	0	–	–
Pulmonary stenosis	+	+	?	0	?	?	+	+	+	+	+	+	+	–	+	+
Tricuspid regurg.	+	0	0	0	?	0	+	+	+	+	0	–	0	–	St.	St.
"Asthmatic attacks"	+	+	+	0	–	–	–	–	–	–	–	?	+	–	–	–
Edema	+	+	0	+	+	+	+	+	+	+	+	+	+	+	+	+
Cyanosis	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Flushes or plethoric discoloration	+	+	+	+	+	+	–	–	+	+	+	+	+	+	+	+
Frequent loose stools	+	+	+	+	–	+	+	+	0	+	+	+	+	0	–	–

+ denotes proved presence of the symptom or lesion; ?, possible but not proved presence of the symptom; –, the symptom neither described nor excluded in the original paper; 0, proved absence of the symptom or finding, and St., tricuspid stenosis.

*E.P. and S.H., still living.

Recently Rosenbaum and associates thought it possible that generalized widening of cutaneous vessels, pulmonary and tricuspid stenosis, and neoplastic liver disease might constitute a clinical syndrome.

The Principal Findings and Symptoms of the Syndrome Presented in Our Series.—

A. 1. Malignant carcinoid of the small intestine with slow progression and metastases to the liver and also to other intra-abdominal organs. Dependent edema, frequent watery stools, borborygmi, and abdominal pain were common symptoms; ascites and pleural effusion more rare.

2. Generalized widening of the small vessels of the skin. In some cases telangiectases. Pellagra-like cutaneous lesions in several cases.

3. Plethoric coloration and total or partial cyanosis in the absence of polycythemia. Peculiar patchy flushing of the skin, in some cases combined with pilomotor symptoms.

B. 4. Pulmonary stenosis of the valvular type and tricuspid regurgitation.

5. Attacks of "bronchial asthma" of a rather unusual type.

The valvular lesions and asthmatic attacks may possibly be initiated by the carcinoid.

CUTANEOUS PHENOMENA

A. Type.—The most outstanding and easily visible findings are those of the skin. Peacock[18] first pointed out that cyanosis is of a reddish-blue tinge in those cases of uncomplicated pulmonary stenosis which develop cyanosis. It comes late and only when decompensation has developed, being a part of this, as shown by Selzer and associates.[19,20] The cutaneous manifestations in our cases, however, are much more varied than those mentioned in other studies of pulmonary stenosis. They include:

(1) Telangiectasis over the bridge of the nose and the cheek; (2) generalized widening of the capillaries and postcapillary veins of the skin (and also of the retina and the heart in Case 1); (3) late developing, localized, brownish, scaly thickening of the skin, somewhat resembling pellagra. It may be caused by the intestinal disfunction which manifests itself with diarrhea in these patients. A short treatment with nicotinic amide (pellagra-preventive factor) in Case 1 prior to his death gave a slight regression. A diet rich in vitamins had no effect in Case 11. (4) The most characteristic symptom, which led to the correct diagnosis in Cases 4, 5 and 16, is a bright to deep purple flush, later mingled with heavily cyanotic and white blotches and very intense brick-red spots, all of these appearing, changing and disappearing.

The cutaneous manifestations in Cases 1, 10, 12, 13, and 14 are detailed in articles 1, 5, 12 and 7, and to some length in our quotations. They do not differ principally from those in Cases 3 or 4, that have been studied with special interest in regard to the general circulatory symptoms accompanying the flushes.

In S.H. (Case 4) they date five years back and had shown steady progression until the carcinoid was excised. Immediately after the operation they decreased in frequency and intensity as did the bowel movements. They consisted of very intense and sudden color changes, for which we think the word "flush" an appropriate term. They will be considered in detail in a separate paper by Waldenström and Ljungberg.[3] It will here only be mentioned that there could be seen four different stages during the flushes. Every flush begins as diffuse reddening of the face and the neck. It then disappears or spreads to the trunk and the extremities. In the third stage sharply demarcated irregular deep red patches stand sharply out against the surrounding skin.

They coalesce in part, often preceded by broad blanched margins. In the fourth stage there are in addition cyanotic patches of varying intensity and localization. They contrast remarkably against the other sharply margined white, deep-red and bright brick-red patches. The different stages vary from flush to flush in intensity and duration but seem in general to follow this outline both in Cases 3 and 4.

B. Direct Studies of the Skin.—Before the operation a difference in skin temperature of 9°C. was registered between adjacent red and white (or cyanotic) patches in this patient. After operation the differences, as registered with the same thermocouple by the same person, have been smaller and less conclusive. In K. G. there were differences of ½ to 1½°C.

The changes in the color of the skin must be caused by changes in the concentration of oxygenated and reduced hemoglobin in the vessels of the skin, above all in those of the subcapillary network.[21]

C. *Discussion of Patho-physiology.*—The different colors seem to represent various stages of contraction or dilatation in both precapillary arteries and capillaries: the hot red patches, dilated arterioles and capillaries; cold cyanotic patches, contracted arterioles and dilated capillaries; and cold white patches, contracted arterioles and capillaries. The unusual brick-red color is not clearly understood. During the generalized red flush, quickened heart rate and large pulse pressure often occur. It somewhat resembles impending shock. Possibly an actual shock is counteracted by reversed vasomotoric reactions in other organs, by draining of blood depots and, in the third and fourth stages, by localized constriction of cutaneous vessels.

Pulmonary stenosis with functionally closed septa is essentially acyanotic, cyanosis appearing only after failure of the right side of the heart has developed.[11,19,20,22] In some of our cases it is clearly shown that cyanosis appeared long before any sign of failure of the right side of the heart. In S. H., moreover, there were no signs indicating any valvular lesion. There is no polycythemia reported among our cases. The patchy distribution of cyanosis cannot readily be explained as caused by pulmonary stenosis or tricuspid insufficiency.

The distribution of color does not follow any nerve trunks or innervatory segments. The sudden onset, changes, and irregular distribution of the "flush" and cyanosis, the recorded vasomotor symptoms and perhaps also the spontaneous statement of S. H., that after a period of extensive flushing there usually follows a period without flush, may indicate a release of vasomotorically active substances. If that would be the case, could they be liberated from the carcinoid?

THE CARCINOIDS

In this paper we are not intending to discuss the frequency, morphology, or genesis of the carcinoids of the intestinal tract. We will leave it an open question whether the carcinoids reported herein differ morphologically or biochemically from other carcinoids.

Waldenström has studied these aspects in the patient S. H. and her reaction to different drugs and chemicals. Biochemical examinations have been made by Prof. U. S. von Euler. These findings and the aspects related to the carcinoids will be discussed in detail by Waldenström and Ljungberg.[3]

We will here only comment briefly on some clinical peculiarities:

The symptomatology has been sparsely reported in the literature about carcinoids. Some cases with carcinoid of the intestinal tract have had periods of frequent and loose stools. Selberg among his fifty-three cases of carcinoids of the small intestine had one patient with diarrhea.[23]

The bulk of the carcinoids however either have been found accidentally on the autopsy table, having given no recorded symptoms, or have given diffuse discomfort in the abdomen increasing to repeated attacks of subileus or ileus, of have been asymptomatic until a diagnosis of acute occlusional ileus of unknown nature has been made. They hardly ever give any melena, as the mucosal layer is uninterrupted.*

Some cases with extensive metastases have shown increasing anemia, ascites, edema, and liver enlargement with or without a palpable abdominal tumor. In these cases an abdominal new growth with metastases has been suspected, but the origin of the tumor has been unknown before exploration.

To our knowledge the patient S. H. is the first patient reported, in which the diagnosis of carcinoid of the small intestine was made before operation, which gives to the "flushing" a therapeutic importance. There are cases of intestinal carcinoid reported which at operation had extensive spread to various organs and yet lived for 10 to 15 years after resection of the intestinal tumor.[17,23] Our patient S. M. had at the time of the ileostomy already symptoms of intestinal obstruction for 20 years. At the autopsy (16 years after the operation) the stricture, already seen at the operation, was shown to be caused by a constricting carcinoid, and this as well as the regional mesenteric metastases had not altered appreciably since the operation.

The sites of metastases are also of interest. About 20 per cent of the carcinoids of the small intestine are said to show metastases.[24] Most of these have, however, spread only to the regional glands in the mesentery. This often gives angulation of the bowel, and this seems to be the mechanism in most of the cases with episodes of ileus, where the tumor itself has not constricted the lumen.

Involvement of the liver and other parenchymatous organs is much less common. In our cases the spread included extensive metastases to the liver in all cases, to the ovaries in all the women, to the pancreas and adrenals in some cases, and is very interesting.

The patient, S. H., had more than 10 watery stools a day prior to operation, upon which there was an immediate drop to 5 to 6 stools of semisolid consistency.

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*An exception to this is E.H. a 67-year-old woman who presents a case history different from the others discussed in this paper. She was hospitalized in 1942 at the Surgical Department of Lund after several episodes of intestinal bleeding. There was found a small carcinoid of the duodenum and a single metastasis in a regional lymph node but no detectable liver metastases. The tumor and metastasis were removed seemingly radically, and she has been in excellent health since. She has never had any abdominal pain or discomfort, diarrhea, borborygmi, flushes, distended superficial veins, asthmatic attacks, or cardiac trouble. She has been studied by us this year with reference to her cardiovascular system. She was found to be in good general condition with normal physical heart findings, electrocardiogram, phonocardiogram, and ballistocardiogram. Arterial blood pressure was 165/100 mm. Hg. This is an example of a patient with repeated bleedings but no signs of increased peristalsis or vascular phenomena prior to operation. At the operation there were no indications of liver enlargement. The operation was thought to be radical, and she has developed neither abdominal nor cardiovascular symptoms of "carcinoidosis" (a name suggested by J.W.)[3] 12 years after the operation.

The flushing decreased in a similar way. The decrease indicates the carcinoid as a cause of these symptoms. The carcinoid of the patient S. M. was situated in that coil of the distal ileum which had been shunted off from the digestive tract by an ileostomy in 1936. This may explain why there was no delay of passage at the roentgenographic examination, and it makes a mechanical irritation less likely to be the cause of the diarrhea. The liberation from the carcinoid of one or more substances causing the hyperperistalsis and vascular phenomena seems plausible.

The liver was studded with metastases in all cases reported here, which seems to indicate that the liver metastases are important factors in the genesis of this syndrome. The mechanisms can be one or more of the following:

1. These carcinoids have a more malignant nature, giving more extensive spread, or the liver has been injured by substances from the carcinoid and offers lessened resistance against new growth.
2. The uninjured liver destroys or eliminates the supposed substance, until the functions of the liver are suppressed, or abnormal shunts between the portal and hepatic veins are formed.
3. The metastases themselves liberate the supposed substance, magnifying the production of it. The consistency of symptoms in S.H. and E.P. after operation may indicate this, but does not prove it.

THE VALVULAR LESIONS

We have no definite proof as to which finding, the carcinoid or the valvular lesions, is the primary, or if they are concomitant. This is due to the insidious onset and progression of both lesions. Since the introduction of heart catheterization and angiocardiography, it has been shown that milder degrees of pulmonary stenosis are more common, and the auscultatory findings may be less pronounced than formerly thought.[22,25] Accordingly the statement that physical examination together with roentgenogram and electrocardiogram in S. H. (and, at earlier hospitalizations in K. G., E. P., S. M. and the patient of Arnett and Long) did not indicate any heart disease, does not exclude some minor stenosis of the pulmonary orifice. A stenosis of such severity as to cause failure of the right side of the heart seems, however, improbable and we believe the edema, ascites, and cyanosis in S. H. to be caused by the tumor with its metastases and not by an undiagnosed pulmonary stenosis.

In those patients of which we have detailed records (that is our own patients) the symptoms to be attributed with certainty to the carcinoid (abdominal discomfort with spasmodic pain and borborygmi, and diarrhea and in S. M. direct visualization of the tumor and mesenterial metastases) preceded any physical sign of pulmonary stenosis by a long time.

What, then, is the genesis of the valvular lesions? There are no direct indications of a congenital origin. In the case reports, none of the patients is reported to have had a diagnosis of heart disease at birth. The lesion in all cases is due to sclerosis and partial fusion of the cusps, to some degree also to narrowing of the lumen of the arterial wall at the insertion. None of them had an infundibular or membranous stenosis or septal defects. Only in S. M. was there a possibly congenital defect of the aortic valves. There was no clubbing, nor a family history of congenital heart disease, nor a history or findings indicating syphilitic

infection. Only S. H. (who has no sign of heart disease) had a history of rheumatic disease with arthritis but no cardiac symptoms.* There have been no major atheromatous or arteriosclerotic findings. Microscopically, the lesions reported are thickening of the endocardium, fibrosis, and vascularization of the valves but no infiltration with inflammatory cells (except in the tricuspid cusps in Cases 2 and 3 and in the pulmonary valves in Case 10) and no Aschoff bodies, except in one of Rosenbaum's cases. The marked hypertrophy of the right ventricular walls contrasts against the low-grade pulmonary stenosis found, which seemingly would produce no valvular resistance at all or only a small resistance in a person with "normal" cardiac output.

The valvular lesions of this series thus seem to differ morphologically and developmentally from other cases of pulmonary stenosis. Probably they form a separate subdivision of the valvular group in the grouping of Keith reviewed by Green and associates[11] and Dow and associates.[22]

Is there any possible explanation of the predominantly right-sided valvular lesions as a result of the action of a hypothetic substance with vasomotor properties originated in carcinoids?

Such an explanation would need experimental studies and long-term observations to be accepted or discarded, but we think it possible, even if the mode of development is hard to prove. Ballistocardiographic studies on the patients E. P. and S. H. (to be published in another paper)[9] indicate a sudden increase of the venous return during the "flush" which possibly indicates a mechanical factor in the pathogenesis.

The so-called "asthmatic attacks", in K. G., S. M. and also, but not so marked, in E. P. are correlated to the flush. As already mentioned they consist of expiratory stridor and dyspnea during the third and fourth stages of "flush". The sudden dyspneic attacks in Case 11 may have been of the same type. They were thought by the physicians in charge to be of bronchial origin, but were rather atypical. None of these patients had any physical signs of heart disease at the time of onset of these attacks. In the patient K. G. who had no disease of the left side of the heart they subsided when the signs of pulmonary stenosis developed. Adrenalin inhalations gave remarkable relief of the dyspnea.

SEARCH FOR A COMMON DENOMINATOR

During the last few years, several groups of investigators have studied vaso-active substances from animal tissues. Works by Page,[26] Reid and Rand,[27] Erspamer,[28] and Comroe and associates[29] should here be mentioned. From these studies have emerged a number of interesting facts relating to a substance found in enterochromaffin tissue and called enteramine by Erspamer and serotonin by Rapport and associates.[30] Chemically, it has been identified as an indole derivative (5-hydroxytryptamine). Among its other vaso-active effects, elevation of the pressure in the pulmonary artery is noted in some animal species, and apparently related to an increase of the vascular resistance in the pulmonary

*At the time of proof-reading the patient S.H. was re-examined and now a harsh systolic murmur, Grade 3 to 4, with maximal intensity over the pulmonary area had developed. Her edema and ascites had disappeared, but instead she had shortness of breath and wheezing respiration on exertion.

bed. Apnea is noted on intravenous injection, and it has also been shown that the substance causes bronchoconstriction. The intestinal peristalsis increases strongly after a short period. We have been unable to find other statements on the cutaneous vessels than those of Erspamer, who mentions that the skin of the rat becomes red after the injections of enteramine. The enteramine is probably rapidly destroyed in normal conditions. If this destruction takes place in the liver, hepatic insufficiency may increase the effects of the substance.

In a recent communication to Nature, Lembeck[31] seems to have given conclusive proof that a carcinoid tumor found at autopsy contained considerable amounts of enteramine. The tumor was extracted with N/50 HCl. It contained 2.5 mg. 5-hydroxytryptamine in 1 gram of tissue.

This fundamental biochemical observation confirms the histologic resemblance between the enterochromaffine cells and the carcinoid.

In our opinion, these findings present the common denominator of most of the signs and symptoms of the syndrome described. Secretion of large amounts of 5-hydroxytryptamine may (not least at a time when liver damage may be present) induce functional changes in the vascular bed (peripheral and pulmonary) which, if sustained for a period of years, may give rise also to organic alterations such as telangiectasis, nutritional disorders of the skin, and apparently also valvular lesions of the heart. The importance of the latter observation for the explanation of the patho-physiology in valvular heart disease is obvious.

GENERAL SUMMARY

1. A new syndrome is described. Seven definite cases, four probable (Cases 11, 12, 13 and 16) and five with partial or not fully verified symptoms (Cases 3, 4, 5, 6 and 14) are presented.

2. The syndrome consists of carcinoid of the small intestine, metastases to the liver, and in several cases to other parenchymatous organs, valvular disease of the right side of the heart without septal defects, sudden flushing of the skin, an unusual type of patchily distributed changing cyanosis, frequent watery stools, "asthma", and, finally, edema and ascites.

3. The cause is believed to be a malignant carcinoid of the small intestine with hormonal properties and extensive metastases to the liver. The pathophysiologic findings are discussed.

4. Among those substances with vaso-active properties at present known, 5-hydroxytryptamine (enteramine or serotonin) is the one which in its effects seems most likely to correspond with the signs and symptoms of the syndrome. It has recently been extracted in considerable amounts from a carcinoid.

5. The syndrome is apparently rare, but if, as shown in the patients S. H. and B. G., persons with "flush" be properly investigated, more cases will probably be discovered and brought to operation.

REFERENCES

1. Biörck, G., Axén, O., and Thorson, Å.: Unusual Cyanosis in a Boy With Congenital Pulmonary Stenosis and Tricuspid Insufficiency. Fatal Outcome After Angiocardiography, Am. Heart J. 44:143, 1952.

2. Waldenström, J., and Ljungberg, E.: Carcinoids and Vasomotoric Symptoms, Svenska Läkartidningen **50**:690, 1953.
3. Waldenström, J., and Ljungberg, E.: Acta med. Scandinav. (In press.)
4. Ljung, O.: Carcinoid Associated With Intense Facial Hyperemia, Nordisk Med. **50**:1143, 1953.
5. Isler, P., and Hedinger, Chr.: Metastasierendes Dünndarmcarcinoid mit schweren, vorwiegend das rechte Herz betreffenden Klappenfehlern und Pulmonalstenose—ein eigenartiger Symptomenkomplex? Schweiz. med. Wchnschr. **83**:5, 1953.
6. Scholte, A. J.: Ein Fall von Angioma teleangiectaticum Cutis mit chronischer Endokarditis und malignem Dünndarmcarcinoid, Beitrag. path. Anat. **86**:440, 1931.
7. Rosenbaum, F. F., Santer, D. G., and Claudon, D. B.: Essential Telangiectasia, Pulmonic and Tricuspid Stenosis, and Neoplastic Liver Disease. A Possible New Clinical Syndrome, (Abst.) J. Lab. & Clin. Med. **42**:941, 1953.
8. Personal communication from Dr. Simon Ståhl, Fritsla, Sweden.
9. Thorson, A.: Cardiodynamic Findings in Persons With Malignant Carcinoids of the Small Intestine and Flushing of the Skin (In preparation).
10. Lepeschkin, E.: Modern Electrocardiography I. Baltimore, 1953, Williams & Wilkins Company.
11. Greene, D. G., Baldwin, E. de F., Baldwin, J. S., Himmelstein, A., Roh, C. E., and Cournand, A.: Pure Congenital Pulmonary Stenosis and Idiopathic Congenital Dilatation of the Pulmonary Artery, Am. J. Med. **6**:24, 1949.
12. Currens, J. H., Kinney, T. D., and White, P. D.: Pulmonary Stenosis With Intact Interventricular Septum; Report of Eleven Cases, Am. Heart J. **30**:491, 1945.
13. Arnett, J. H., and Long, C.: A Case of Congenital Stenosis of the Pulmonary Valve, With Late Onset of Cyanosis: Death From Carcinoma of the Pancreas, Am. J. M. Sc. **182**:212, 1931.
14. Feyrter, F.: Carcinoid und Carcinom, Ergebn. d. allg. Path. u. path Anat. **29**:305, 1934.
15. Cassidy, M. A.: Abdominal Carcinomatosis, With Probable Adrenal Involvement, Proc. Royal Soc. Med. **24**:139, 1930.
16. Cassidy, M. A.: Postmortem Findings in Case Shown on October 10, 1930, as one of Abdominal Carcinomatosis With Probable Adrenal Involvement, Proc. Royal Soc. Med. **24**:920, 1931.
17. Cassidy, M. A.: Abdominal Carcinomatosis Associated With Vasomotor Disturbances, Proc. Royal Soc. Med. **27**:220, 1934.
18. Peacock, T. B.: Malformations of the Human Heart, ed. 2, London, 1866, John Churchill and Sons.
19. Selzer, A., Carnes, W. H., Noble, C. A., Jr., Higgins, W. H., Jr., and Holmes, R. O.: The Syndrome of Pulmonary Stenosis With Patent Foramen Ovale, Am. J. Med. **6**:3, 1949.
20. Selzer, A., and Carnes, W. H.: The Role of Pulmonary Stenosis in the Production of Chronic Cyanosis, Am. Heart J. **45**:382, 1953.
21. Greenwood, W. F., Barger, A. C., Di Palma, J. R., Stokes, J., III, and Smith, L. H.: Factors Affecting the Appearance and Persistence of Visible Cutaneous Reactive Hyperemia in Man, J. Clin. Investigation **27**:290, 1948.
22. Dow, J. W., Levine, H. D., Elkin, M., Haynes, F. W., Hellems, H. K., Whittenberger, J. W., Ferris, B. G., Goodale, W. T., Harvey, W. P., Eppinger, E. C., and Dexter, L.: Studies of Congenital Heart Disease. IV. Uncomplicated Pulmonic Stenosis, Circulation **1**:267, 1950.
23. Selberg, W.: Ueber das Carcinoid des Darmes, Virchows Arch. f. path. Anat. **306**:467, 1940.
24. Gatch, W. D.: In Christopher's Textbook of Surgery, ed. 4, Philadelphia, 1946, W. B. Saunders Company, p. 1018.
25. Maraist, F., Daley, R., Draper, A., Jr., Heimbecker, R., Dammann, F., Jr., Kieffer, R., Jr., King, J. T., Ferencz, C., and Bing, R. J.: The Physiological Findings in 34 Patients With Isolated Pulmonary Valvular Stenosis, Bull. Johns Hopkins Hosp. **88**:1, 1951.
26. Page, I. H.: The Vascular Action of Natural Serotonin, 5- and 7-Hydroxytryptamine and Tryptamine, J. Pharmacol. & Exper. Therap. **105**:58, 1952.
27. Reid, G., and Rand, M.: Physiological Actions of the Partially Purified Serum Vasoconstrictor (Serotonin), Australian J. Exper. Biol. & Med. **29**:401, 1951.
28. Erspamer, V.: Il Sistema Cellulare Enterocromaffine e l'enteramina. Rendiconti Scientifici farmitalia I, 1954.
29. Comroe, J. H., Jr., van Lingen, B., Stroud, R. C., and Roncoroni, A.: Reflex and Direct Cardiopulmonary Effects of 5-OH-Tryptamine (Serotonin), Am. J. Physiol. **173**:379, 1953.
30. Rapport, M. M., Green, A. A., and Page, I. H.: Partial Purification of the Vasoconstrictor in Beef Serum, J. Biol. Chem. **174**:735, 1948.
31. Lembeck, F.: 5-Hydroxytryptamine in a Carcinoid Tumour, Nature **172**:910, 1953.

PULMONARY CIRCULATION TIME, ELBOW-LEFT VENTRICLE AND ELBOW-RIGHT VENTRICLE CIRCULATION TIMES, OBTAINED BY MEANS OF FLUORODENSOGRAPHY WITH RADIOPAQUE SUBSTANCE

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FLUORODENSOGRAPHY with a radiopaque substance is a diagnostic hemodynamic method devised by us at the National Institute of Cardiology. Based on the fact that the main curves in the tracing of the cardiac chambers are to be attributed to changes in density produced by the emptying and filling of the chambers in each cardiac cycle, we have been able to prove that the introduction of an opaque substance into the blood stream increases the amplitude of the waves, which are quite apparent in the fluorodensogram and are synchronous with the arrival of the substance to the chamber under study.[1]

Fig. 1, after Wiggers,[2] shows a ventricular volume curve simultaneously registered with a phonocardiogram. The vertical lines divide the curve in segments corresponding to the different stages of the cardiac cycle. Systole is included from *A* to *F* and it is subdivided into the following periods: A-C isometric contraction; C-D rapid emptying periods; D-F slow ejection period. The diastolic stage from *F* to *K* is made up of the following periods: F-G is the beginning of diastole; G-H, isometric relaxation; H-I, rapid filling; I-J, slow filling or diastasis; J-K, auricular contraction. The modifications obtained in the fluorodensogram with the injection of an opaque substance are seen in the descending branch C-F and in the ascending branch H-J of the ventricular curve depending on the changes in density which take place during ejection and ventricular filling. Those due to other factors such as isometric contraction and relaxation and rotation of the heart do not change.

In this paper we apply the method under study to determine the circulation time from the right elbow to the right ventricle, from the right elbow to the left ventricle and the pulmonary circulation time. The number of cardiac cycles during which the changes in the tracing remained unaltered are discussed. Fig. 2 shows the tracing which measures the elbow-left ventricle and elbow-right ventricle circulation time in one of our cases.

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MATERIAL AND METHOD

Twenty-one subjects were analyzed, nineteen with ages between 17 and 44 years. One of the cases was a 12-year-old boy. They all were considered normal. Another case was that of a 75-year-old man with an aneurysm of the pulmonary artery.

The equipment used consists of the following elements:

A. A device for the injection of radiopaque substance made of a set for intravenous infusions, a 10 c.c. syringe; a 3-way stopcock, and an 18-gauge needle, 2½ cm. long.

B. A fluoroscope of the usual type.

C. A Sanborn electrokymograph adapted to half waves which uses an RCA phototube No. 931A.

D. A Sanborn's Stetho-Cardiette electrocardiograph.

E. In each instance, 4 c.c. of the radiopaque substance (Winthrop's Diodrast 70 per cent) were injected intravenously.

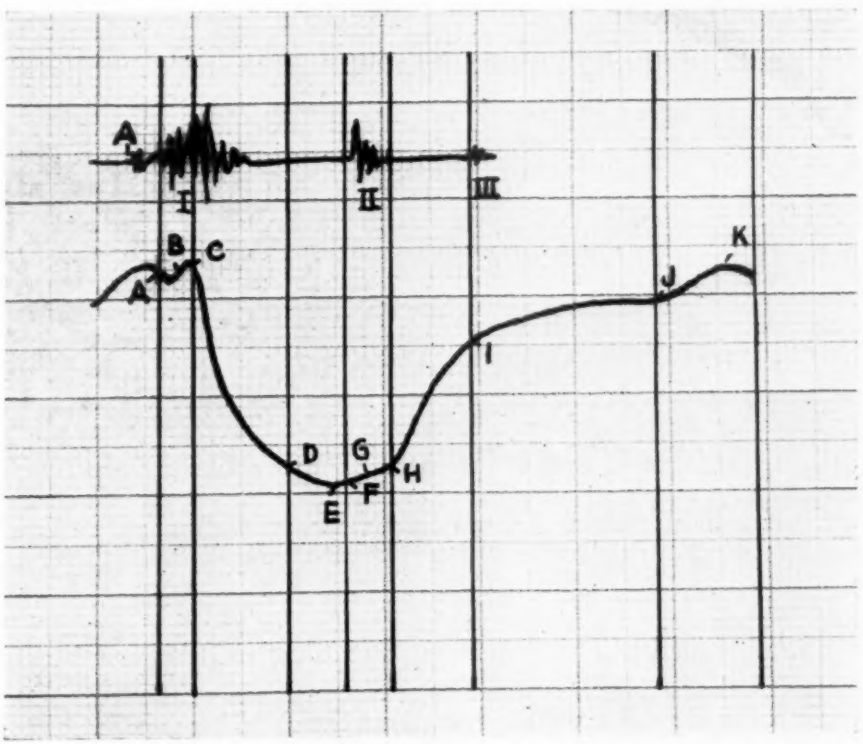

Fig. 1.

The following details were checked:

(a) Between 2 and 3 ma. and 65 kv. were used for fluoroscopy.

(b) Patients were upright, in the left anterior oblique position.

(c) Diodrast was injected in the vein of the right elbow. Both the beginning and the end of the injection were indicated in the tracing by the person who gave it with the aid of the microphone of the Stetho-Cardiette. This was accomplished by pronouncing the letters A and B, respectively.

(d) The tracing was taken during postinspiratory apnea.

(e) The speed of the tracing was 25 mm. per second. The string had a sensitivity of 5 mm. per millivolt.

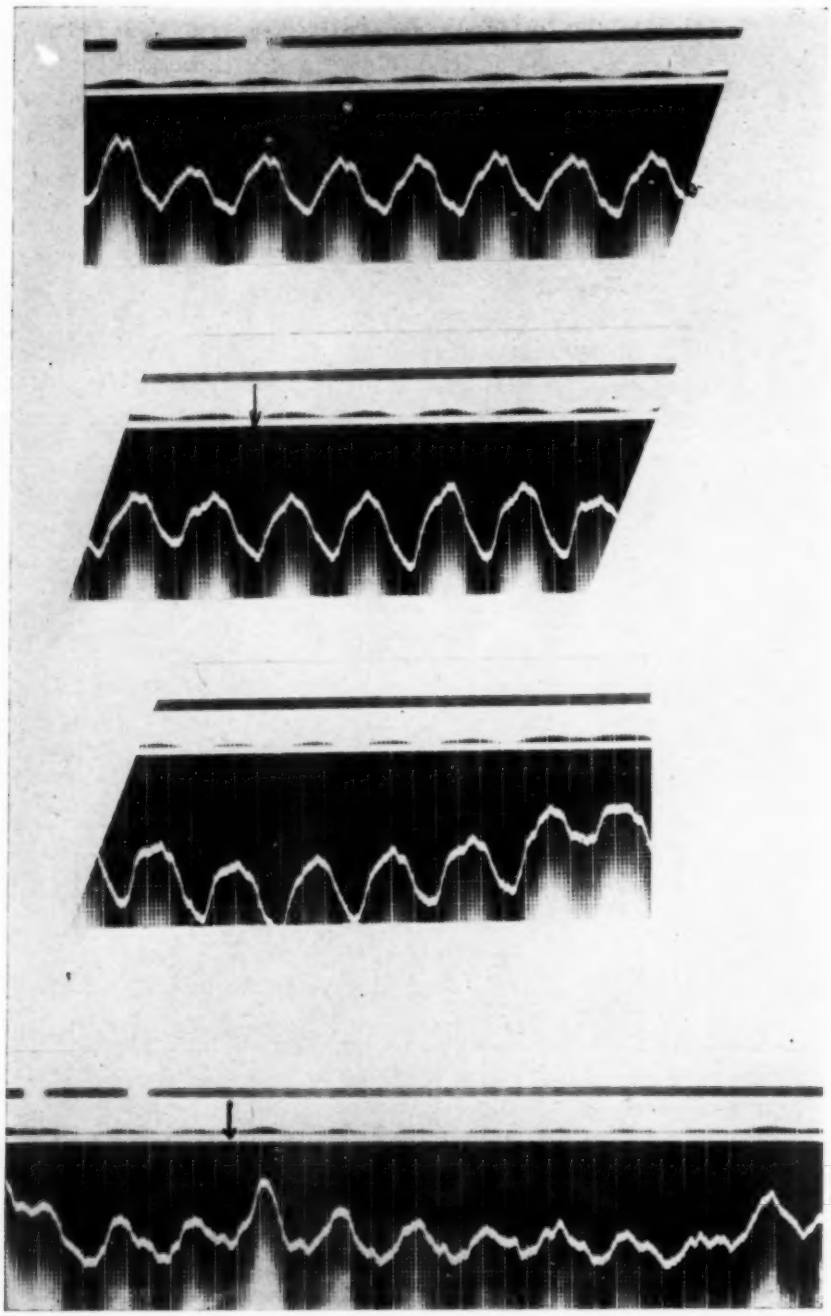

Fig. 2.—Circulation time elbow-left ventricle and elbow-right ventricle determined in the same person, 6 minutes and 1.32 minutes, respectively.

(f) The amplifying capacity of the selector was placed in position No. 3.

(g) For the interpretation of the tracing the elapsed time from the point coincident with the middle of the distance between the beginning and the end of the injection to the moment the first changes appear in the curve is measured.

(h) The circulation times from elbow to right ventricle and elbow to left ventricle were measured individually and, by subtracting the former from the latter, the pulmonary circulation time was obtained. With the use of the double cell, all of these values could be measured simultaneously with a single injection of radiopaque substance.

RESULTS

The circulation times of nineteen normal adults (Table I) were as follows: The elbow-left ventricle circulation time gave a mean figure of 5.61 seconds with a standard deviation of ±0.59, the extreme values being 6.90 and 4.40. The mean value obtained for the elbow-right ventricle was 1.63 with a standard deviation of ±0.23 and extreme values of 2.08 and 1.28. The pulmonary circulation time in each case gave a mean value of 3.98 with a standard deviation of ±0.61 and extreme values of 5.14 and 2.88 seconds.

In the 12-year-old normal boy the elbow-left ventricle circulation time was 5.52 seconds, the elbow-right ventricle circulation time 1.64 seconds, and the pulmonary circulation time 3.88.

In the 75-year-old patient with a pulmonary artery aneurysm, the elbow-left ventricle circulation time was 41 seconds; the elbow-right ventricle circulation time was 4.2 seconds and the pulmonary circulation time 36.8 seconds. These figures are quite illustrative and of great value for the angiocardiogram. Indeed, this study was done in this patient and the first plate was taken 18 seconds after the injection at which time the right chambers and the pulmonary artery were filled; the left chambers on the contrary were not visualized yet. In a second study, considering the elbow-left ventricle circulation time according to our method, the plates were taken at the end of 38 seconds with which the left chambers and the aorta were very clearly visualized.

The base line of the tracing was uniform in all of the registrations for normal subjects. In the pathologic case the base line was considerably displaced upward.

The modifications of the tracing in the measurement of the elbow-right ventricle circulation time lasted 1 to 3 cycles with a mean of 1.68 cycles and a standard deviation of ±0.58. The measurement of the elbow-left ventricle circulation time was maintained during 3 to 7 cycles with an average of 5.16 cycles and a standard deviation of 1.17. It was impossible to ascertain the duration in the pathologic case due to the fact that the patient also had auricular fibrillation.

COMMENTS

As seen in Table I, the values of the different circulation times have a standard deviation with respect to the average which are valid for statistical purposes.

In the 12-year-old patient the values found are within the limits for adults. The same can be said for the distance between the elbow and the sternum measured in centimeters from the elbow to the midsternal line. In the pathologic case the delay in the elbow-right ventricle circulation time may be accounted for by the great venous hypertension; the increase in the elbow-left ventricle circula-

tion time would be due to the delay produced by stagnation of the blood within the aneurysm of the pulmonary artery.

The duration of the changes in the curve along several cardiac cycles different from the right to the left ventricle may be attributed to the following facts:

(a) The blood with the opaque substance reaches the right cardiac chambers rapidly through vessels of large caliber such as the superior vena cava. On the

TABLE I

N	AGE	SEX	BL	ES	E-LV	E-RV	PC	E-LVc	E-RVc
34564	44	F	Uniform	40	5.84	1.28	4.56	6	1
34617	43	F	Uniform	41	4.88	1.68	3.20	4	2
34616	41	F	Uniform	40	5.60	2.00	3.60	4	1
34299	41	F	Uniform	46	5.31	1.70	3.61	3	1
34445	40	F	Uniform	40	4.40	1.52	2.88	5	2
Without Number	38	M	Uniform	45	5.08	1.68	3.40	6	2
Without Number	33	M	Uniform	41	6.00	1.44	4.56	6	3
34379	32	M	Uniform	42	6.16	2.00	4.16	6	1
34547	32	F	Uniform	40	5.20	1.40	3.80	5	2
34458	31	F	Uniform	37	5.84	1.60	4.24	4	2
34562	27	F	Uniform	40	5.84	1.52	4.32	6	2
34400	26	F	Uniform	41	6.00	1.32	4.68	6	2
Without Number	22	M	Uniform	44	6.90	1.76	5.14	4	1
34476	20	M	Uniform	47	6.40	1.60	4.80	6	2
Without Number	20	F	Uniform	37	5.00	1.44	3.56	6	2
34472	19	F	Uniform	42	5.40	1.80	3.60	6	1
Without Number	19	F	Uniform	40	5.50	2.08	3.42	5	1
34300	17	M	Uniform	46	6.00	1.65	4.35	3	2
Without Number	17	F	Uniform	38	5.20	1.52	3.68	7	2
Highest and lowest figures					4.40 6.90	1.28 2.08	2.88 5.14	3–7	1–3
Mean					5.61	1.63	3.98	5.16	1.68
Standard deviation					±0.59	±0.23	±0.61	1.17	±0.58

N = Registration numbers
BL = Base line
ES = Elbow-sternum distance in centimeters
E-LV = Elbow-left ventricle circulation time
E-RV = Elbow-right ventricle circulation time
PC = Pulmonary circulation time
E-LVc = Numbers of cardiac cycles with graphic modifications of the elbow-left ventricle circulation time
E-RVc = Numbers of cardiac cycles with graphic modifications of the elbow-right ventricle circulation time

contrary, the blood reaches the left chambers in a slow and gradual manner coming from the network of the lung. These conditions may influence the time used by either ventricle to empty itself of the opaque substance.

(b) The factor of diffusion of the opaque substance in the blood must be proportional to the distance to be traveled in order to reach a given cardiac chamber. Thus, the opaque substance would be much less diffused in the right ventricle than in the left ventricle, and this would obviously favor the greater speed with which the right ventricle empties the opaque substance in a smaller number of contractions.

As we learn more about this new method we will undoubtedly find that other factors may influence the number of contractions used by each ventricle to rid itself of the opaque substance. We are convinced that with this method the time during which the substance remains within each cardiac chamber will be most useful for the study of the residual volume of the cavities under normal and pathologic conditions. The fact that the base line of the tracing was uniform in all of the normal cases and was displaced in the abnormal case would be evaluated in the light of a greater number of observations.

SUMMARY

The authors studied the circulation time from the right elbow to the right ventricle, right elbow-left ventricle, and pulmonary circulation times by fluorodensography with radiopaque substance.

The study was performed in twenty-one normal subjects: nineteen with ages between 17 and 44 years, and a boy of 12. A pathologic case was also studied.

The equipment utilized is described in detail as well as the standardization of the various instruments and the technique for the recording and interpretation of the tracings.

The circulation times obtained were: elbow-left ventricle, 5.61 seconds (mean value), with ±0.59 standard deviation; elbow-right ventricle, 1.63 seconds with a standard deviation of ±0.23; pulmonary circulation time, 3.98 seconds, with a standard deviation of ±0.61. In the case with an aneurysm of the pulmonary artery the circulation time from elbow to left ventricle was 41 seconds; elbow-right ventricle, 4.2 seconds; and the pulmonary circulation time, 36.8 seconds.

A comparative study is made on the different number of cycles that show changes in the circulation time tracings from elbow to left ventricle and elbow-right ventricle.

An analysis is made on the results obtained in the pathologic case.

REFERENCES

1. Moros, G., Neri, R., and Villagordoa, G.: Fluorodensography With Radiopaque Substance. A New Method for Hemodynamic Investigation, AM. HEART J. 45:495, 1953.
2. Wiggers, J.: Circulatory Dynamics, New York, 1952, Grune & Stratton, Inc., p. 54.

BLOOD VOLUME IN CONGESTIVE HEART FAILURE AS DETERMINED WITH IODINATED HUMAN SERUM ALBUMIN

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BLOOD volume alteration in congestive heart failure has been studied by many investigators.[1-14,37] Gibson and Evans remarked 15 years ago, "Changes in blood volume in cardiac decompensation reported in the literature are of a conflicting nature".[4] Subsequent investigations have intensified the conflict rather than resolved it, so that one may now quote the literature to demonstrate decreased, increased, or normal blood volume in congestive failure. Further quotation will reveal that in recovery from decompensation, blood volume may decrease, increase, or not change at all. Evidence compiled by the authors does not supply an answer to this confusion; however, an attempt is made to evaluate some phases of this complex problem.

In general, dye techniques show increased blood volume in cardiac decompensation. The dye method of Keith and associates[34] led to the concept of "plus" and "minus" decompensation as elaborated by the studies of Wollheim[2] and Goldbloom and Libin.[3] Patients in what may be interpreted as right heart failure were hypervolemic, while that group symptomatic of left heart failure was hypovolemic; the latter group was found to have an increase of blood volume toward normal on recovery.

Gibson and Evans,[4] using the dye T-1824 method, reported an increase in blood volume as decompensation progressed. The increase was more marked in the red cell mass than in plasma volume, with a resultant hemoconcentration, and bore a direct relationship to venous pressure and circulation time. On recovery, the plasma volume decreased most rapidly leading to a further elevation of hematocrit, which later returned toward normal as compensation was maintained. The trend toward normovolemia was more often partial than complete. In this series no patient was observed who failed to show a diminution in blood volume with compensation.

Seymour and associates,[6] using the dye T-1824, concluded that whole blood volume decreased by 25 per cent and plasma volume by 35 per cent in patients who recovered from congestive heart failure. Recovery was associated with increased cardiac output, serum protein concentration, and an elevation in hematocrit.

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Meneely and Kaltreider,[7] using the same technique, report a substantial increase in blood volume in patients with congestive failure. The increased volume in the decompensated state may be predominantly contributed to by the plasma or the red cells; neither component was more consistently elevated. Circulation time and venous pressure were not directly related to blood volume. There was a high degree of correlation between anoxemia and red cell mass. This observation is in accord with Waller and associates,[5] who noted an elevated cell volume in decompensation which decreased on compensation; the improved clinical state was associated with elevated bilirubinemia, increased fecal urobilin, and a decreased reticulocyte count. Such changes may reflect hemolysis and bone marrow depression with improved oxygenation.

Warren and Stead[8] demonstrated a direct correlation in congestive failure between increased blood volume and salt ingestion, and conversely, a diminished blood volume with diuresis. They conclude that "Increase in plasma volume . . . is one mainfestation of the increase in the amount and pressure of the extracellular fluid which is caused by the defective excretion of salt and water." Consequently, enhanced plasma volume would elevate venous pressure, and plasma protein concentration initially decreased by dilution would increase and preserve the effective osmotic pressure.

DiPalma and Kendall,[9] using Evans blue dye, reported two types of blood volume response to therapy. One variety showed a marked decrease in an initially high blood volume. This decrease was accompanied by first a decrease in hematocrit and plasma specific gravity; as compensation proceeded the hematocrit and specific gravity returned to approximately initial levels while blood volume continued to fall. The second type of response showed little elevation or change in blood volume, nor was there a marked alteration in hematocrit or specific gravity.

Labeling red cells with P^{32} using the method of Hevesy and Zerahn,[35] Nylin[10] reported a fall of 28 per cent in whole blood volume and a decrease of 18 per cent in red cell mass during recovery from congestive failure. Nylin and Hedlund[12] subsequently reported on blood volume in seven cases of cardiac decompensation. In six cases, repeated determinations were made during or following therapy. These authors conclude, "In decompensated cardiac patients there is not only an increase in the total quantity of blood and plasma; but also in the amount of erythrocytes. After compensation is restored, both the plasma and blood corpuscles decrease in quantity."

Ross and associates[13] compared circulating blood volumes in congestive failure with controls using P^{32} tagged red cells and the dye T-1824. They conclude, ". . . there is no significant increase in the circulating blood volume in patients with congestive heart failure over controls as determined with the tagged cell method." Ross and associates[37] have reported recently on this work in more detail. They could not demonstrate in this particular group of patients an increased blood volume using P^{32} tagged red cells or a decrease on compensation. However, Evans blue dye determinations showed an increase of 25 per cent over normal and a decrease of 18.6 per cent on becoming compensated. In addition, thirty-five cases of congestive heart failure were reported

while decompensated; of these, fourteen cases were repeated when compensated. Vital capacity increased from 1.7 liters to 2.4 liters during compensation in the latter series of patients. It is postulated that the distended venous system in congestive failure is secondary to a redistribution of blood from the small vessels to the larger veins. Further suggestion is made that the small vessel hematocrit is probably increased in comparison to venous hematocrit in congestive failure. No satisfactory experimental evidence is cited to support this contention. During the process of compensation no increase in hematocrit was noted. This is contrary to the observations made by previous investigators[4,9] and in our own observations.

Prentice and associates,[14] using the P^{32} tagged cell technique, report on twenty-seven cases of congestive failure. Twelve of these patients had normal blood, red cell, and plasma volume. Of this group five had no peripheral edema, two had minimal, two moderate and three marked peripheral edema. Three of the cases were postmyocardial infarction in minimal failure. One case had chronic glomerulonephritis for a period of six years. In fifteen cases either blood, red cell, or plasma volume was increased. Seven cases had no peripheral edema, two had minimal, three moderate and three marked peripheral edema. Seven cases had rheumatic valvulitis and showed marked elevation of total blood volume, red cell volume, and plasma volume. The two components were equally elevated. In six cases repeated determinations of blood volume when compensated revealed an elevation of blood volume in five instances and a decrease in one case. Serum sodium concentration did not change in congestive heart failure but total body sodium showed a marked increase.

METHOD*

Blood volume was determined with iodinated human serum albumin. Two modifications of this technique were employed in the present study. Earlier determinations using iodinated human serum albumin employed the method of Crispell and associates[26] which was reported in detail in a previous publication.[38] Aliquots of iodinated human serum albumin were dialyzed at intervals to determine the presence of free I^{131}; significant quantities were never found. No determination was made to ascertain if the albumin had become denatured. Recently, a more rapid method has been used, in which whole blood activity was counted in the "Marinelli beaker." In the latter technique, human serum albumin labeled with 40 to 50 microcuries of I^{131} activity was diluted to 30 c.c. in physiologic saline. Twenty cubic centimeters of this mixture were administered intravenously from a calibrated syringe. At 10, 20, and 30 minute intervals 12 c.c. of venous blood were withdrawn from the contralateral arm into a syringe made wet with heparin; withdrawal was effected without stasis. Ten cubic centimeters of blood were counted in a "Marinelli beaker" using a bismuth cathode G. M. tube and a "Nuclear-Chicago" scaler. Five cubic centimeters of the original solution were diluted to 1,000 c.c. in a volumetric flask and 10 c.c.

*Radioactive iodinated human serum albumin was prepared by Abbott Laboratories, North Chicago, Ill. The radioactive iodine was obtained from the Atomic Energy Commission.

of this standard mixture counted as above. Whole blood volume is calculated by this formula.

$$\text{Whole blood volume} = \frac{\text{Counts per c.c. of iodoalbumin injected} \times \text{Volume of iodoalbumin injected}}{\text{Counts per c.c. of whole blood}}$$

Hematocrit from individual blood samples was determined by centrifugation at 3,000 r.p.m. for 30 minutes in a stoppered Wintrobe tube. Plasma trapping was corrected by a factor of 0.915. All patients had cardiomegaly; in almost all instances the patients were dyspneic, gave a history of orthopnea, and had hepatomegaly. They showed evidence or pulmonary congestion and peripheral edema. Ascites and pleural effusion were noted in some instances.

Blood volume determination was made within several hours of admission, after the patient had been at rest. Repeated determination was made after the patient had become compensated under the standard therapy of low-salt diet, digitalization, rest, and diuretics. The repeat determinations were made at rest about three to four hours after a light meal.

Venous pressure was determined through an 18-gauge needle in the antecubital vein at a level 10 cm. from the back in those individuals of normal size, using a citrate-filled spinal manometer. Arm-to-tongue circulation time was determined by the subjective method using 5 c.c. of desoxycholate solution.

RESULTS

Blood volume determinations in thirty-two male patients, with repeat determinations in twenty-five patients, are summarized in Tables I and II.

Evaluation of values determined is dependent upon comparison with "normal" values. In our laboratory using iodintated human serum albumin, normal males have been tested and the values arrived at agree well with other reports using albumin labeling techniques.

WBV = 73 c.c./kg. standard body weight
PV = 43 c.c./kg. standard body weight
TPRCV = 30 c.c./kg. standard body weight

Blood, plasma, and cell volume* in the patients studied was calculated on the basis of the patient's weight when decompensated and also on the basis of his weight when compensated. The deviation from the normal volume for these weights is expressed as per cent variation from 100 per cent of normal value. This was done to make comparison of the individual cases more easy. The weight when compensated no doubt represents a more physiologic level for those cases previously in congestive failure.

In sixteen of the thirty-two cases, weight when compensated after therapy was available. On the basis of this weight WBV, TPRCV, and PV were elevated above normal in all instances (Table III). TPRCV was most elevated with mean deviation of 64.6 per cent above normal, WBV was elevated an average

*WBV = Whole blood volume
PV = Plasma volume
TPRCV = Total packed red cell volume

TABLE I. CLINICAL DATA IN THIRTY-TWO MALE PATIENTS IN CONGESTIVE HEART FAILURE

PATIENT	CLINICAL STATUS*	AGE	ETIOLOGY†	PULSE	BLOOD PRESSURE	VENOUS PRESSURE, CM.	CIRCULATION TIME, SEC.	RHYTHM‡	EDEMA	ASCITES	LUNGS, RÂLES	EFFUSION, PLEURAL	LIVER, CM.	DYSPNEA AT REST	DYSPNEA ON EXERTION
1. A.P.	D	61	R	100	130/100	17	45	S	+++	0	+	0	0	+	++
	C	—	—	76	136/60	18	46	S	0	0	+	0	0	+	++
2. W.S.	D	74	HT AS	92	180/120	—	—	AF	+++	0	+	+	3	++	++
3. J.F.	D	62	L	106	150/90	—	—	AF	++++	0	+	+	7	+++	+++
4. C.K.	D	55	AS	60	132/60	26	39	AF	++++	+	+	+	25	+++	+++
	C	—	—	72	100/80	17	—	AF	?	+	0	+	10	0	+
5. H.B.	D	52	HT AS	78	135/105	22	65	S	++++	+	+	0	?	+++	+++
	C	—	—	76	—	21	83	S	0	0	0	0	0	0	++
6. H.M.	D	54	HT	112	190/140	—	—	S	+	0	+	0	8	++	++
7. W.S.	D	59	HT AS	96	150/100	11	65	S	++	0	+	0	2	++	++
8. W.N.	D	48	HT AS	110	154/100	22	64	S	++	0	0	+	9	+	++
	C	—	—	72	120/84	4	27	S	0	0	0	0	0	0	0
9. P.J.	D	64	HT AS	120	160/120	16	52	S	++++	0	+	0	6	++	++
10. E.B.	D	60	R	80	130/80	—	—	AF	++	0	0	0	4	++	+++
11. S.C.	D	59	HT	100	170/120	22	45	S	++	0	+	0	6	+++	+++
12. L.C.	D	59	AS	96	120/100	—	—	S	—	0	—	0	—	—	—
	C	—	—	—	—	—	—	S	—	0	—	0	—	—	—
13. H.P.	D	45	P HT	100	140/90	15	18	S	++++	0	+	0	3	++	+++
	C	—	—	88	112/60	8	18	S	0	0	0	0	0	0	++
14. V.L.	D	63	AS	132	140/100	27	—	AF	++++	+	+	0	6	++	+++
	C	—	—	86	150/100	8	—	AF	0	0	0	0	2	0	0
15. F.A.	D	31	L	88	144/30	—	—	AF	+++	0	+	0	5	++	+++
16. C.R.	D	53	AS	84	122/80	17	—	S	++	0	+	0	4	+	+++

16. C.R.	D	53	AS	84	122/80	17	—	S	++	0	+	0	4	+	+++
	C	—	—	76	126/74	9	—	S	0	0	0	0	0	0	0
17. P.S.	D	59	HT	100	170/120	104	42	S	+	0	+	0	4	+++	+++
18. G.I.	D	46	R	138	130/70	—	—	AF	++	0	0	0	5	+++	+++
	C	—	—	88	—	—	—	AF	0	0	0	0	1	0	++
19. A.S.	D	58	HT AS	104	240/130	20	55	AF	++++	0	0	0	6	++	+++
20. R.M.	D	60	AS	104	120/84	27.5	38	S	++++	0	+	+	7	+++	+++
21. H.P.	D	60	AS	84	130/80	—	—	S	++++	0	+	+	6	++	+++
22. P.C.	D	57	HT	140	194/140	24	—	AF	++	+	+	0	4	0	++
	C	—	—	80	184/96	8	—	AF	0	0	0	0	0	0	0
23. W.H.	D	58	AS	108	140/100	23	48	S	++	0	+	0	0	+	++++
	C	—	—	96	145/80	4	15	S	0	0	0	0	0	0	+
24. F.A.	D	32	L	98	140/44	30	—	AF	++++	0	+	0	8	+++	+++
	C	—	—	86	140/40	—	—	AF	+	0	0	0	6	+	++
25. J.L.	D	55	HT	80	170/100	24	20	S	++++	+	0	0	5	++	+++
26. J.H.	D	42	AS	100	110/90	—	—	S	0	0	+	0	4	0	++
27. F.P.	D	64	HT AS	108	170/120	20	45	S	++++	0	+	+	4	+++	+++
	C	—	—	92	135/85	7	50	S	0	0	0	0	—	0	0
28. J.F.	D	62	AS	104	150/92	13	25	S	++	0	+	0	5	++	+++
29. G.B.	D	58	AS	84	130/90	—	—	S	+	0	+	0	3	0	++
30. R.R.	D	45	AS	110	126/106	26	63	S	+++	0	+	0	11	+++	+++
	C	—	—	80	110/82	7	—	S	0	0	0	0	0	0	0
31. F.C.	D	63	AS	80	130/90	—	—	AF	++	0	+	0	3	0	++
32. N.H.	D	61	HT	94	184/94	17	45	S	+	0	+	0	5	0	++
	C	—	—	76	—	Norm	Norm	S	0	0	0	0	—	0	0

*D: Patient decompensated in congestive failure; C: Patient compensated after therapy.
†HT: Hypertensive heart disease; AS: Arteriosclerotic heart disease; R: Rheumatic heart disease; L: Luetic heart disease; PHT: Pulmonary hypertension.
‡S: Sinus rhythm; AF: Auricular fibrillation.

TABLE II. DATA ON HEMATOCRIT, WEIGHT, AND BLOOD VOLUME AND ITS COMPONENTS IN THIRTY-TWO MALE PATIENTS IN CONGESTIVE HEART FAILURE
REPEATED DETERMINATIONS ARE NOTED IN TWENTY-FIVE CASES FOLLOWING THERAPY

PATIENT	CLINICAL STATUS	HEMATO-CRIT	WEIGHT, KG.	BLOOD VOLUME			RBC VOLUME			PLASMA VOLUME			INTERVAL, (DAYS)
				C.C.	WET WEIGHT (%)	DRY WEIGHT (%)	C.C.	WET WEIGHT (%)	DRY WEIGHT (%)	C.C.	WET WEIGHT (%)	DRY WEIGHT (%)	
1. A.P.	D	50	66.36	8000	+65.2	+73.5	3656	+83.6	+92.9	4344	+52.1	+59.9	—
	C	50	63.18	7644	+57.8	+65.7	3531	+77.3	+86.3	4113	+44.0	+51.4	15
2. W.S.	D	45.5	60.45	6988	+58.4	—	2879	+58.8	—	4109	+58.0	—	—
3. J.F.	D	46.0	100.00	11466	+57.1	—	4827	+60.9	—	6639	+54.4	—	—
4. C.K.	D	47	80.45	9184	+56.4	+78.6	3949	+63.7	+86.9	5235	+51.3	+72.8	—
	C	43	70.45	9048	+54.1	+75.9	3583	+48.5	+69.6	5465	+58.0	+80.4	60
5. H.B.	D	54	80.91	8889	+50.5	+86.0	4381	+80.5	+123.2	4508	+29.6	+60.2	—
	C	60.5	65.45	7533	+27.5	+57.7	4173	+71.9	+112.6	3360	+3.7	+19.4	43
6. H.M.	D	40	72.73	7924	+49.3	+71.6	2900	+33.0	+52.8	5024	+60.7	+84.6	—
	C	45	63.28	6570	+23.8	+42.2	2523	+15.7	+32.9	4047	+29.4	+48.2	23
7. W.S.	D	42.5	65.90	6793	+41.2	—	2615	+32.3	—	4178	+47.4	—	—
	C	43	—	6183	+28.5	—	2430	+22.9	—	3753	+32.4	—	8
8. W.N.	D	49.5	65.90	6687	+39.0	+57.5	3029	+53.2	+73.6	3658	+29.1	+38.2	—
	C	53	58.18	4885	+1.5	+15.0	2369	+19.8	+35.8	2516	−11.2	0.0	13
9. P.J.	D	50.5	82.27	8319	+38.5	—	3827	+55.1	—	4492	+27.0	—	—
	C	51.0	—	8968	+49.3	—	4188	+69.7	—	4780	+35.1	—	27
10. E.B.	D	50.5	59.18	5980	+38.4	—	2751	+55.0	—	3229	+26.9	—	—
	C	54.5	—	6196	+43.4	—	3067	+72.8	—	3129	+22.9	—	10

11. S.C.	D	50.5	78.64	7881	+37.3	—	3641	+54.3	—	4240	+25.4	—	—
	C	53.5	—	6541	+13.9	—	3210	+36.1	—	3334	−1.4	—	33
12. L.C.	D	45	68.18	6803	+36.7	+46.5	2803	+37.1	+46.8	4000	+36.4	+46.2	—
	C	45	63.63	7010	+40.8	+50.9	2853	+39.5	+49.4	4157	+41.8	+51.9	27
13. H.P.	D	54	62.73	6188	+35.1	+54.1	3057	+62.4	+85.3	3131	+16.1	+32.5	—
	C	51	55.00	5854	+27.8	+46.8	2757	+46.5	+67.1	3097	+14.8	+31.1	24
14. V.L.	D	49	79.55	7667	+32.0	+56.1	3435	+44.0	+70.2	4232	+23.7	+46.3	—
	C	47.5	67.27	7444	+28.2	+51.6	3238	+35.7	+60.5	4206	+22.9	+45.4	18
15. F.A.	D	47.5	69.09	6568	+30.2	—	2857	+37.8	—	3711	+24.9	—	—
	C	42	—	5661	+12.2	—	2174	+4.9	—	3487	+17.4	—	27
16. C.R.	D	56	70.00	6777	+32.0	+49.1	3409	+62.3	+82.5	3368	+11.9	+25.8	—
	C	57	62.27	5780	+13.1	+27.1	3017	+43.7	+61.5	2763	−12.7	+3.2	14
17. P.S.	D	51	79.00	7568	+31.2	—	3534	+49.1	—	4034	+15.8	—	—
18. G.I.	D	49.5	89.55	8444	+29.0	+39.0	3825	+42.4	+53.3	4619	+19.9	+22.6	—
	C	56	83.18	6303	−3.6	+3.8	3227	+20.2	+29.3	3076	−20.2	−14.0	12
19. A.S.	D	44.5	93.18	8607	+26.6	—	3503	+25.3	—	5104	+27.4	—	—
	C	43.5	—	9068	+33.3	—	3609	+29.1	—	5457	+36.2	—	56
20. R.M.	D	52	79.55	7333	+26.3	—	3490	+46.3	—	3843	+12.3	—	—
21. H.P.	D	42.5	100.00	8966	+22.8	—	3488	+16.3	—	5478	+27.4	—	—
22. P.C.	D	50	75.00	6389	+16.7	+44.8	2926	+30.0	+61.4	3463	+7.4	+33.2	—
	C	54	60.45	5014	−8.4	+13.6	2477	+10.1	+36.6	2537	−21.3	−2.4	13
23. W.H.	D	42.5	77.73	6600	+16.3	+51.9	2567	+10.0	+43 7	4033	+20.7	+57.5	—
	C	59	59.54	5372	−5.3	+23.6	2901	+24.4	+62.4	2471	−26.1	−3.5	8

TABLE II. DATA ON HEMATOCRIT, WEIGHT, AND BLOOD VOLUME AND ITS COMPONENTS IN THIRTY-TWO MALE PATIENTS IN CONGESTIVE HEART FAILURE REPEATED DETERMINATIONS ARE NOTED IN TWENTY-FIVE CASES FOLLOWING THERAPY (CONTINUED)

PATIENT	CLINICAL STATUS	HEMATOCRIT	WEIGHT, KG.	BLOOD VOLUME			RBC VOLUME			PLASMA VOLUME			INTERVAL (DAYS)
				C.C.	WET WEIGHT (%)	DRY WEIGHT (%)	C.C.	WET WEIGHT (%)	DRY WEIGHT (%)	C.C.	WET WEIGHT (%)	DRY WEIGHT (%)	
24. F.A.	D	48	68.64	5815	+16.0	+43.7	2553	+24.0	+53.5	3262	+10.5	+36.8	—
	C	48.5	55.45	4282	−14.5	+5.8	1901	−7.6	+14.3	2381	−19.3	0.0	10
25. J.L.	D	49.5	98.64	8287	+15.1	—	3729	+26.0	—	4558	+7.5	—	—
	C	53	—	8167	+13.4	—	3920	+32.5	—	4247	0.0	—	20
26. J.H.	D	47	82.27	7139	+10.5	—	3070	+2.1	—	4069	+16.3	—	—
27. F.P.	D	52	65.00	5200	+9.6	+31.7	2475	+26.9	+52.5	2725	−2.5	+17.5	—
	C	54	54.09	4809	+1.3	+21.8	2376	+21.8	+46.4	2433	−13.0	+4.6	22
28. J.F.	D	45.5	70.00	5524	+8.1	—	2320	+10.4	—	3204	+6.5	—	—
	C	50	—	5531	0.0	—	2544	+21.1	—	2987	−1.0	—	13
29. G.B.	D	46.5	79.55	62.19	+7.1	—	26.49	+11.0	—	3570	+4.4	—	—
30. R.R.	D	53.5	62.27	4741	+4.3	+19.1	2342	+25.4	+43.2	2399	−10.4	+2.3	—
	C	56	54.55	4494	−1.1	+12.9	2301	+23.2	+40.6	2193	−18.1	−6.5	33
31. F.C.	D	43	79.55	5867	+1.0	—	2288	−4.1	—	3579	+4.6	—	—
	C	42	—	6635	+14.3	—	2521	+5.7	—	4114	+20.3	—	15
32. N.H.	D	47.5	84.09	5980	−2.6	+5.4	2601	+3.0	+11.5	3379	−6.6	+1.1	—
	C	54	77.72	4880	−19.7	−14.0	2391	−5.2	+2.5	2489	−31.2	−25.5	13

of 50.5 per cent, and PV elevation mean was 39.9 per cent above normal. In thirty-two cases, on the basis of weight when decompensated (wet weight), nearly all volumes were elevated above normal. TPRCV was increased 37.8 per cent above normal, WBV 29.3 per cent, and PV 23.0 per cent. Were these values corrected for the retained edema fluid they would no doubt show a degree of deviation similar to that of those cases calculated on the basis of weight when compensated.

An attempt was made to relate the increase in volume to various other observed factors in the decompensated state. There was no consistent relationship of degree of increase in volume to the etiology of the heart disease. In general, the most severely decompensated patients showed the highest volumes. Venous pressure showed a trend toward a direct relation to WBV and PV. Circulation time, though elevated, was not increased in proportion to the blood volume. The hematocrit determination averaged 48.2, and in some instances was elevated above normal. Few, if any, cases showed a decrease in hematocrit below the normal range.

TABLE III. MEAN VALUE FOR BLOOD VOLUME COMPONENTS IN CONGESTIVE HEART FAILURE, EXPRESSED AS PERCENTAGE DEVIATION FROM NORMAL VALUES

		WBV	TPRCV	PV	HEMATOCRIT
On basis of decompensated weight	Decompensated (32 Cases)	+29.3	+37.8	+23.0	48.2
	Compensated (25 Cases)	+17.3	+31.2	+8.1	50.6
On basis of compensated weight	Decompensated (16 Cases)	+50.5	+64.6	+39.9	
	Compensated (16 Cases)	+31.3	+50.5	+18.5	

Results of therapy leading to a more or less compensated state showed definite trends. PV, WBV, and TPRCV decreased. The greatest decrease was in PV; the smallest in TPRCV (Table IV). Plasma volume in those cases with the least increase returned to normal or subnormal levels. Those cases with the highest plasma volume decreased, but not to normal. In five of thirty-two cases an increase in PV occurred with compensation. These patients in most instances responded slowly to therapy and an interval of 30 to 60 days was noted before they reached a relatively stable, though partially compensated, state.

TABLE IV. MEAN CHANGES IN RECOVERY FROM CONGESTIVE FAILURE, EXPRESSED IN PERCENTAGE, CALCULATED ON THE BASIS OF VALUES WHEN DECOMPENSATED

25 CASES				16 CASES
WBV	TPRCV	PV	HEMATOCRIT	WEIGHT
−8.8	−5.0	−11.6	+4.6	−13.3

TPRCV in many instances showed a marked decrease on compensation, in some instances amounting to 30 per cent of the circulating red cell volume. Most cases show a slight to moderate decrease in TPRCV. In seven of twenty-five cases an increase was noted. One such case (Case 23, Tables I and II) displayed a precipitous drop in plasma volume; during the eight day period of compensation the hematocrit rose from 42.5 to 59. It would be of interest to know the relationship of venous to small vessel hematocrit in such cases and whether a true change in TPRCV is represented. The P^{32} tagged cell studies of Ross and associates[37] included no cases with significant increase in hematocrit on recovery from congestive failure. A similarity in change of TPRCV during therapy was noted in Cases 15 and 24, F. A., Tables I and II. This 32-year-old man had syphilitic heart disease with aortic insufficiency. During his initial admission (15, Table II), while compensating, his TPRCV decreased by 683 c.c.; during a subsequent admission (24, Table II), his TPRCV decreased by 652 c.c.

Change in TPRCV is of interest when the time rate of change is considered. Table V contains the change in TPRCV per day as calculated by dividing the total change during the period of compensation by the number of days necessary to arrive at the compensated state. This figure may be compared to the daily destruction, assuming a 120-day life for the erythrocyte. In the normal individual, no change in TPRCV should be observed, and the figure represents the equilibrium between erythropoiesis and destruction. Several of the cases imply a more rapid rate of destruction than would normally occur if regeneration of red cells were completely arrested.

TABLE V. DAILY CHANGE IN TPRCV DURING COMPENSATION

PATIENT	TOTAL CHANGE IN TPRCV IN CC	TIME OF TREATMENT IN DAYS	CHANGE IN TPRCV PER DAY	EXPECTED RATE OF RBC DESTRUCTION PER DAY
1	−125	15	−8.3	30.5
4	−366	60	−6.1	32.9
5	−208	43	−4.6	36.3
6	−377	23	−16.4	24.2
7	−185	8	−23.1	21.8
8	−660	13	−57.7	25.2
9	+361	27	+13.4	31.9
10	+316	10	+31.6	22.7
11	−431	33	−13.1	30.3
12	+50	27	+1.8	23.4
13	−300	24	−12.5	26.5
14	−197	18	−10.9	28.6
15	−683	27	−25.3	23.8
16	−392	14	−28.1	28.4
18	−598	12	−49.8	31.8
19	+106	56	+1.9	29.2
22	−449	13	−34.5	24.4
23	+334	8	+41.7	21.4
24	−652	32	−23.7	21.3
25	+191	20	+9.5	31.1
27	−99	22	−4.5	20.6
28	+222	13	+17.1	19.3
30	−41	33	−1.2	19.5
31	+367	15	+24.5	19.1
32	−210	13	−16.9	21.7

Hematocrit values increased on compensation in sixteen of twenty-five cases; a mean increase in hematocrit of 4.6 per cent was noted in the twenty-five cases. In the eight instances in which the hematocrit remained the same or decreased, nearly all the patients were characterized by an increase in plasma volume. Most of these individuals had arteriosclerotic heart disease with systemic hypertension.

Of the twenty-five cases reported, all lost weight on treatment. The mean decrease in weight in this group was 13.3 per cent of that observed when entering the hospital. The highest degree of correlation was noted between change in weight and change in plasma volume; poor correlation was seen in comparing weight change to TPRCV change.

DISCUSSION

Validity of the particular techniques employed in determining circulating blood volume must be appreciated in interpreting existing knowledge of such values in congestive heart failure. Most early measurements determined plasma volume by dilution of an intravenous injection of a dye which formed a complex with albumin. Circulating blood volume and red cell mass were extrapolated from the peripheral venous hematocrit. Dynamics of capillary circulation alters small vessel hematocrit so that such extrapolation is now warranted. Ebert and Stead found the small vessels richer in plasma and poorer in red cells than the venous blood in six normal males. Determinations were made on the small vessels of the arm and revealed an 8 per cent decrease in hemoglobin.[15] Fahraeus,[16] studying blood flow in small tubes, demonstrated concentric laminar lag of plasma at the periphery and transport of red cells at more rapid rate in the axial flow, resulting in a decreased hematocrit. Gibson and associates[17] state, "Seventeen per cent of the total whole blood volume is within the minute vessels . . . of the normal dog under light morphine narcosis." The above value does not account for blood in the small vessels of the mesentery, skin and subcutaneous tissue, or of the bone marrow. Neither can this information be interpreted to suggest, as Prentice and associates[14] have done, that the same percentage of circulating blood volume or the same small vessel hematocrit exist in the small vessels of a patient in congestive heart failure. Under conditions of increased venous pressure, tissue hypoxia, and fluid retention, the small vessels may well contain an appreciable quantity of plasma-diluted blood, thereby effectively lowering total body hematocrit as compared to venous hematocrit.

Direct comparison of blood volume determination by dye methods and labeled red cells have almost uniformly demonstrated higher values with the former technique.[18-24] Comparison of blood volumes determined with I^{131} tagged human serum albumin have been comparable to or somewhat less than the volumes obtained by the dye method.[25,26] Factors other than hematocrit which have been considered in comparing dye to cell techniques are the escape of dye from circulating blood to the lymphatic system, phagocytosis by the reticuloendothelial system,[27,28] and loss of dye into the bile.[29] There is little likelihood of iodinated human serum albumin behaving as a colloidal dye and being influenced by the last two factors. Escape of dye and serum albumin from the

circulation does occur; however, the rate must be slow and the percentage small within the time allowed for mixing in determining blood volume. Transfer of albumin across capillary membranes is not of such magnitude that 12 to 25 per cent of the circulating albumin is lost to the lymph in 30 to 60 minutes. Dye could not be detected in edema fluid of patients or edematous dogs after injection of high concentration of the dye T-1824.[4,30] Human serum albumin tagged with I^{131} was not observed to accumulate in edema fluid of chronic congestive heart failure in detectable quantities within 30 minutes, using a very sensitive scintillation counter; neither was appreciable activity found in the urine (less than 1 per cent in three hours).[31] Protein concentration in edema fluid is of a low order in congestive failure[32] and in anoxemia of chronic pulmonary disease.[8] This is observed despite the possibility of poor lymphatic return in congestive failure.[33]

On the basis of present information no absolute conclusions are admissible concerning values for blood volume or its components in congestive heart failure, nor can we make such conclusions relevant to volume changes during therapy leading to compensation. Present controversies may be somewhat resolved when it is realized that labeled red cells with proper mixing measure circulating red cell space, and that labeled albumin determines circulating plasma space plus a small but variable and presently poorly defined distribution outside of the vasculature. With proper technique in the hands of careful workers, the respective blood volume components may be measured with reasonable accuracy, using P^{32} labeled erythrocytes and I^{131} labeled human serum albumin. Studies presently being investigated will further clarify this controversy. First, consideration should be given to the determination of small vessel hematocrit and the precentage of circulating blood volume present in these small vessels during congestive heart failure. Second, the survival of erythrocytes must be adequately determined in recovery from congestive failure by labeling cells and by adequate determination of pigment turnover. Relation of the later study to the secondary polycythemia of hypoxia should be more clearly delineated.

SUMMARY

1. Blood volume was determined in thirty-two cases of congestive heart failure. Repeat determination was made in twenty-five of the patients after treatment leading to compensation. Human serum albumin labeled with I^{131} was used in making these studies.

2. Blood volume was elevated above normal in those cases studied. Total packed red cell volume was more markedly elevated than plasma volume.

3. In response to therapy the plasma component was more labile and decreased more rapidly than the cellular component. Hematocrit increased with therapy.

4. During recovery from congestive heart failure the rate of apparent destruction of erythrocytes exceeded, in some instances, the expected calculated rate of destruction.

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REFERENCES

1. Thompson, W. O.: Studies in Blood Volume. I. The Blood Volume in Myxedema, With a Comparison of Plasma Volume Changes in Myxedema and Cardiac Edema, J. Clin. Investigation **2**:477, 1925-26.
2. Wollheim, E.: Zirkulierende Blutmenge, Kompensation und Dekompensation des Kreislaufes, Verhandl. Deutsch. Gesellsch. inn. Med. **41**:352, 1929.
3. Goldbloom, A. A., and Libin, I.: Clinical Studies in Circulatory Adjustments. I. Clinical Evaluation of Studies of Circulating Blood Volume, Arch. Int. Med. **55**:484, 1935.
4. Gibson, J. G., II, and Evans, W. A., Jr.: Clinical Studies of the Blood Volume. III. Changes in Blood Volume, Venous Pressure and Blood Velocity Rate in Chronic Congestive Heart Failure, J. Clin. Investigation **16**:851, 1937.
5. Waller, J. V., Blumgart, H. L., and Volk, M. C.: Studies of the Blood in Congestive Heart Failure, With Particular Reference to Reticulocytosis, Erythrocyte Fragility, Bilirubinemia, Urobilinogen Excretion and Changes in Blood Volume, Arch. Int. Med. **66**:1230, 1940.
6. Seymour, W. B., Pritchard, W. H., Longley, L. P., and Hayman, J. M., Jr.: Cardiac Output, Blood and Interstitial Fluid Volumes, Total Circulating Serum Protein and Kidney Function During Cardiac Failure and After Improvement, J. Clin. Investigation **21**:229, 1942.
7. Meneely, G. R., and Kaltreider, N. L.: A Study of the Volume of the Blood in Congestive Heart Failure. Relation to Other Measurements in Fifteen Patients, J. Clin. Investigation **22**:521, 1943.
8. Warren, J. V., and Stead, E. A., Jr.: Fluid Dynamics in Chronic Congestive Heart Failure. An Interpretation of the Mechanisms Producing the Edema, Increased Plasma Volume and Elevated Venous Pressure in Certain Patients With Prolonged Congestive Failure, Arch. Int. Med. **73**:138, 1944.
9. DiPalma, J. R., and Kendall, P. E.: The Relationship Between Blood Volume and Blood Specific Gravity in the Recovery From Cardiac Decompensation, J. Lab. & Clin. Med. **29**:390, 1944.
10. Nylin, G.: Blood Volume Determination With Radioactive Phosphorus, Brit. Heart J. **7**:81, 1945.
11. Perera, G. A.: The Increased Plasma Volume in Cardiac Insufficiency: Its Correlation With Right-sided Failure, J. Clin. Investigation **24**:708, 1945.
12. Nylin, G., and Hedlund, S.: Weight of the Red Blood Corpuscle in Heart Failure Determined With Labeled Erythrocytes During and After Decompensation, Am. Heart J. **33**:770, 1947.
13. Ross, J. F., Baker, W. H., and Freis, E. D.: The Blood Volume in Congestive Heart Failure, J. Clin. Investigation **29**:842, 1950.
14. Prentice, T. C., Berlin, N. I., Hyde, G. M., Parsons, R. J., Lawrence, J. H., and Port, S.: Total Red Cell Volume, Plasma Volume and Sodium Space in Congestive Heart Failure, J. Clin. Investigation **30**:1471, 1951.
15. Ebert, R. V., and Stead, E. A., Jr.: Demonstration That the Cell Plasma Ratio of Blood Contained in Minute Vessels is Lower Than That of Venous Blood, J. Clin. Investigation **20**:317, 1941.
16. Fahraeus, R.: The Suspension Stability of the Blood, Physiol. Rev. **9**:241, 1929.
17. Gibson, J. G., II, Seligman, A. M., Peacock, W. D., Aub, J. D., Fine, J., and Evans, R. D.: The Distribution of Red Cells and Plasma in Minute Vessels of the Normal Dog, Determined by Radioactive Isotopes of Iron and Iodine, J. Clin. Investigation **25**:848, 1946.
18. Hahn, P. F., Ross, J. F., Bale, W. F., Balfour, W. M., and Whipple, G. H.: Red Cell and Plasma Volumes (Circulating and Total) as Determined by Radio Iron and by Dye, J. Exper. Med. **75**:221, 1942.
    ____Am. J. Physiol. **136**:314, 1942.
    ____Ibid., **141**:363, 1944.
19. Gibson, J. G., II, Peacock, W. C., Seligman, A. M., and Sack, T.: Circulating Red Cell Volume Measured Simultaneously by the Radioactive Iron and Dye Methods, J. Clin. Investigation **25**:838, 1946.
20. Barnes, D. W. H., Loutit, J. F., and Reeve, E. B.: A Comparison of Estimates of Circulating Red Blood Cell Volume Given by the Ashby Marked Red Cell Method and the T1824-Haematocrit Method in Man, Clin. Sc. **7**:135, 1948.
21. Nachman, H. M., James, G. W., III, Moore, J. W., Evans, E. I., Hayes, E., and Largen, T.: A Comparative Study of Red Cell Volumes in Human Subjects With Radioactive Phosphorus Tagged Red Cells and T-1824 Dye, J. Clin. Investigation **29**:258, 1950.
22. Wassermann, L. R., Yoh, T., and Rashkoff, I. A.: Blood Volume Determination: Comparison of T-1824 and P^{32} Labelled Red Cell Methods, J. Lab. & Clin. Med. **37**:342, 1951.

23. Scott, H. W., Jr., Elliott, S. R., II, and Clay, R. C.: Blood Volume in Congenital Cyanotic Heart Disease: Simultaneous Measurements With Evans Blue and Radioactive Phosphorus, Bull. Johns Hopkins Hosp. **89**:121, 1951.
24. Armin, J., Grant, R. T., Pels, H., and Reeve, E. B.: The Plasma and Blood Volume of Albino Rabbits as Estimated by the Dye (T-1824) and P^{32} Marked Cell Methods, J. Physiol. **116**:59, 1952.
25. Storaasli, J. P., Krieger, H., Friedell, H. L., and Holden, W. D.: The Use of Radioactive Iodinated Plasma Protein in the Study of Blood Volumes, Surg., Gynec. & Obst. **91**:458, 1950.
26. Crispell, L. R., Porter, B., and Nieset, R. T.: Studies of Plasma Volume Using Human Serum Albumin Tagged With Radioactive Iodine^{131}, J. Clin. Investigation **29**:513, 1950.
27. Ferrebee, J. W., Leigh, O. C., and Berliner, R. W.: Passage of the Blue Dye T-1824 From the Blood Stream Into the Lymph, Proc. Soc. Exper. Biol. & Med. **46**:549, 1941.
28. Cardozo, E. L.: The Disappearance of the Blue Dye T-1824 From the Blood Stream Into the Thoracic Duct Lymph, Arch. néerl. de physiol. **25**:410, 1941.
29. Miller, A. T., Jr.: Excretion of the Blue Dye, T-1824, in the Bile, Am. J. Physiol. **151**:229, 1947.
30. Evans, W. E., Jr., and Gibson, J. G., II: The Blood Volume in Diuresis. A Study Employing the Collodial Blue Dye, T-1824, in Dogs Rendered Edematous by Plasmapheresis, Am. J. Physiol. **118**:251, 1937.
31. Kaplan, E.: Unpublished data.
32. Bramkamp, R. G.: The Protein Content of Subcutaneous Edema Fluid in Heart Disease, J. Clin. Investigation **14**:34, 1935.
33. McMaster, P. D.: The Lymphatics and Lymph Flow in the Edematous Skin of Human Beings With Cardiac and Renal Disease, J. Exper. Med. **65**:373, 1937.
34. Keith, N. M., Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume, Arch. Int. Med. **16**:547, 1915.
35. Hevesy, G., and Zerahn, K.: Determination of the Blood Corpuscle Content, Acta physiol. scandinav. **4**:376, 1942.
36. Oshray, E., and Schmidt, C.: Uptake and Excretion Measurements and Their Significance, Brookhaven Conference Report, Radioiodine, July, 1948.
37. Ross, J. F., Chodos, R. B., Baker, W. H., and Freis, E. D.: The Blood Volume in Congestive Heart Failure, Tr. A. Am. Physicians **65**:75, 1952.
38. Kruger, S., Baker, L., and Mosiman, W. D.; Repeated Blood Volume Determinations in Bleeding Peptic Ulcer, Gastroenterology **21**:516, 1952.

"PRIMARY" AMYLOIDOSIS

A Report of Two Cases

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SINCE the original work on amyloidosis by Rokitansky,[1] Virchow,[2] and Wilks,[3] approximately seventy cases of primary amyloidosis have been reported up to July, 1950.[4]

Although it is customary to classify this entity into: primary amyloidosis (etiology unknown), secondary amyloidosis (following a known disease), and amyloidosis following multiple myeloma because of its "primary" distribution, such classification has little or no justification, either from the morphologic or etiologic standpoint. It has been repeatedly shown that cases of so-called primary amyloidosis have a distribution which is considered classical for secondary amyloidosis and vice versa. In primary or idiopathic amyloidosis organs other than the heart and muscles are affected.[5,6] The most frequently encountered primary amyloidosis is that in the heart. Primary amyloidosis of the kidneys is rather infrequent; only a few cases have been reported.[7,8]

We have had occasion to follow two proved cases of primary amyloidosis: one was of the heart and the other of the kidneys.

CASE REPORTS

Case 1.—The first admission of this 55-year-old white man was in August of 1949, at which time he was in cardiac decompensation. He improved on the usual cardiac regimen consisting of digitalis, diuretics, and salt-free diet. The second admission was in February of 1950 with the chief complaint of back and right knee pain for a day and a half. The patient had an episode of temporary aphasia several weeks prior to this admission.

Physical examination: Physical examination revealed a thin, well-developed adult who was slightly dyspneic and who appeared to be acutely ill. There was a small palpable nodule in the right lobe of the thyroid gland. The eye grounds showed Grade 2 retinal sclerosis. There were a very few scattered râles in both bases posteriorly. The heart was enlarged to percussion. The blood pressure was 105/84 mm. Hg. The pulse was 100. The right lower extremity distal to the knee was cold on palpation, and there were areas of purplish discoloration over the dorsum of the foot and ankle. The right calf appeared to be slightly swollen and painful to palpation. The right femoral artery pulsation was palpable but the right popliteal and posterior tibialis and dorsalis pedis could not be felt. Several petechiae were present over the right shoulder and right

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anterior-superior portion of the chest. The temperature was normal on the day of admission but the next day it rose to 101°F. and remained elevated throughout the course of hospitalization.

Laboratory findings: X-ray of the chest showed congestion of both lung fields. The electrocardiogram showed T-wave inversion of the limb leads and Q waves and flattened T waves in precordial Leads V_4, V_5 and V_6, suggestive of a lateral wall infarct. The red blood count was 4,100,000. The white blood count was 16,400 with a normal differential. The hemoglobin was 12 grams. Urinalysis revealed 3+ albumin, trace of sugar, a few granular and hyalin casts, and 10 to 12 white blood cells per high-power field. Nonprotein nitrogen was 50 mg. per cent. Urea was 27.8 mg. per cent; total protein, 7.4; albumin, 4.2; globulin, 3.2; A/G ratio, 1.3. Prothrombin time was 22 seconds (39 per cent of normal); coagulation time, 14 minutes, 35 seconds; serologic reaction was negative; sedimentation rate, 35. The blood culture was negative. A diagnosis of arteriosclerotic heart disease with cardiac decompensation and embolism of the right femoral and popliteal arteries was made.

Hospital course: The patient's temperature continued to remain elevated. Amputation of his right leg was considered. Suddenly, on Feb. 7, 1950, the patient's temperature rose to 103.4°F. Amputation of the right lower extremity was performed, but the patient became incoherent, disoriented, and expired on Feb. 9.

Post-mortem examination: The lungs showed a few areas of bronchopneumonia and exuded a purulent material. The heart weighed 540 grams. There was no pericardial effusion present. There were no valvular lesions present. A diffuse zone showing white, fibrous tissue and measuring 1½ cm. in the greatest diameter was encountered in the wall of the left ventricle near the septum posteriorly. The coronary arteries showed relatively mild atheromatous changes. The left auricular appendage contained an extensive clot. The aorta was relatively free of atheromatous changes. The spleen weighed 180 grams and contained a large infarct. The duodenum showed the presence of five ulcerated zones. The liver weighed 1,700 grams and contained several small infarcts. The right kidney weighed 200 grams; the left, 220. They were firm in consistency. The capsule stripped with ease. The cut surface showed a distinct cortical medullary junction. Infarcted areas were found near the capsule. The adrenals were of usual size and shape. The cut section showed no abnormalities. The medulla was more prominent than usual. The bone marrow was of the usual red color. The remainder of the gross examination was not remarkable.

Microscopic examination: The epicardium and endocardium were thickened and contained masses of dense, pink-staining material. The same pink material accompanied many vessels lying within the wall. In another instance it appeared adjacent to the vessels. The small vessels appeared quite thickened because of this pink-staining material which also appeared in the valve studied. The lumen of the left atrium showed an extensive clot made up of dense, hyaloid fibrin. The lungs showed bronchopneumonia and pulmonary infarction. One section of the spleen showed an infarcted area. No pink-staining material was seen in the spleen. Sections of the liver showed coagulation necrosis and considerable fibrosis. Several small vessels in the portal spaces contained smooth, pink-staining material which resembled that noticed in the heart. Many of the small vessels of the pancreas also showed masses of homogeneous pink-staining material in the walls. The second section showed the same homogeneous pink-staining material in the walls of the larger vessels. The small vessels of the capsules of the adrenals showed the same amyloid material. One section of the kidneys showed the presence of a few hyalinizing glomeruli and the larger vessels showed the presence of homogeneous pink-staining material in the wall and also small collections of amyloid in the fibrous tissues. Special stains for amyloid were made. Sections of the heart studied with this stain showed the presence of amyloid in the vessel walls and in the tissue adjacent to the vessels. There was also a small collection of amyloid in the fibrous tissue. The homogeneous pink-staining material noted on the hematoxylin-eosin stain gave a positive stain for amyloid. Amyloid was identified in the following locations: arteries and veins of the liver; vessels and muscles of the duodenum; vessels of the pancreas and interlobular fibrous tissue of the pancreas; vessels of the adrenals; and vessels of the kidneys. There was also considerable amyloid deposition in the vessels of the lungs.

Final diagnoses: Primary amyloidosis of the heart; deposition of amyloid in the vessels of the liver, duodenum, pancreas, right adrenal, kidney and mural thrombus of the left auricle;

infarction of the myocardium; infarction of the spleen, liver, brain, and lungs; terminal bronchopneumonia; multiple duodenal ulcers; chronic passive congestion of the liver; and encephalomalacia.

CASE 2.—This 53-year-old white man was admitted to the hospital on April 10, 1952, with the chief complaint of swelling of the abdomen which was noted for the first time in October, 1951. The swelling progressed slowly despite medication. There was also mild dyspnea and swelling of the legs.

Past history: In 1948, this patient had a left ureteral calculus which became lodged a few inches above the bladder. Surgical removal became necessary, following which a stricture developed, necessitating another operation consisting in transplantation of the left ureter into a new site of the bladder.

Physical examination: Physical examination revealed an acutely and chronically ill patient. There was marked pallor and generalized edema was noted. The blood pressure was 90/60 mm. Hg. There was a precordial friction rub over the apical area. There was dullness to percussion over both lung bases. The abdominal wall was markedly edematous and a fluid wave was elicited. The liver, spleen, and kidneys could not be palpated because of the ascites. There was four-plus edema of the lower extremities.

Laboratory examinations: X-ray of the chest showed fluid in both lung bases. A scout film of the abdomen revealed a normal gas pattern. The kidneys were not visualized. There was evidence of ascites present. The red blood count was 5,110,000; hemoglobin, 110 per cent; white count, 10,400. Cholesterol on admission was 872. Nonprotein nitrogen was 52. Serum sodium was 125.9 mEq. Potassium was 3.8 mEq. Chlorides were 89 mEq.; creatinine, 1.8; organic phosphorus, 4.8; uric acid, 4.9; inorganic phosphorus, 3; total protein, 4.3; albumin, 1.2; globulin, 3.1; A/G ratio, 0.4; serology negative; urinalysis 4+ albumin, numerous white blood cells, granular and hyalin casts and a few red blood cells. Specific gravity ranged from 1.010 to 1.014. Liver function tests showed 48 per cent of dye retained. Cephalin flocculation test was 1+ after 48 hours; icteric index, 10; cholesterol ester ratio, 57 per cent; Van den Bergh test, direct 0.2, indirect 0.9; serum bilirubin, 1.1; thymol turbidity, 6 units.

Hospital course: During the patient's hospital stay numerous laboratory examinations were performed and they were essentially like the first ones. The patient received numerous transfusions of plasma and protein and an attempt was made to keep the electrolytes within normal limits. The patient expired on May 11, 1952.

Post-mortem examination: The abdominal cavity contained approximately 3,000 c.c. of straw-colored fluid. The right pleural cavity contained approximately 1,500 c.c. of turbid straw-colored fluid and the left chest cavity contained approximately 2,000 c.c. The heart size was within normal limits. The pericardial sac contained the usual amount of clear, straw-colored fluid. The heart, the aorta, and the vessels did not show any abnormality. The spleen weighed 240 grams. It was also extremely firm. The adrenals were normal in size and consistency. There were generalized ecchymoses in the submucous area of the entire gastrointestinal tract, most marked in the stomach and ileum. The right kidney weighed 220 grams, the left 260. The capsules stripped readily revealing a fine to granular surface. Both organs were firmer than normal. The normal color of the freshly sectioned surface was replaced by a pinkish-tan, translucent color. in which there were many yellow-gray flecks. Many petechial hemorrhages were noted within the pelvis of both kidneys. The bladder showed an occlusion of the normal left ureteral orifice and the ureter emptied into the bladder 3 cm. above the normal position. The heart revealed a diffuse, low-grade increase in interstitial fibrous tissue.

Microscopic examination: A moderate degree of amyloid deposition was found in the myocardium within the vascular walls. Sections of the lungs stained for amyloid showed a minimal amount of amyloid deposit within the vascular walls. Sections of the spleen revealed a normal splenic capsule, but the entire architecture of the spleen had been replaced by high-grade amyloid deposition within the vascular walls. The pancreas showed a moderately advanced deposition of amyloid tissue throughout the section. The usual pancreatic architecture was preserved. There was also considerable amyloid deposition within the vascular walls. The duodenum showed

a low-grade amyloid deposition in the blood vessels of the submucosa. The adrenals showed a high-grade amyloid deposition throughout the sections of the adrenal gland. There was also an amyloid deposition within the vascular wall. Sections of the kidney showed normal capsules and occasional minute subcapsular scarring was noted accompanied by low-grade lymphocytic infiltration. Approximately 98 per cent of all the glomeruli were involved by high-grade amyloid deposition, and a patchy type of distribution of amyloid deposition was noted within the interstitial portion of the sections.

Final diagnoses: Primary amyloidosis of the kidneys, spleen and liver; generalized edema; ascites; bilateral hydrothorax; submucosal hemorrhages of the gastrointestinal tract.

DISCUSSION

The heart is the most common site to be affected by primary amyloidosis. Skeletal muscle involvement is much less frequent. Amyloidosis of the tongue with macroglossia may be present in 33 per cent of the cases, according to Dahlin. In this event a biopsy will readily establish the diagnosis.

The Congo red test is positive only if there is liver involvement since the dye is trapped first in the liver. Only rarely are positive Congo red tests obtained when amyloidosis is not found in the liver.[9] Therefore, in predominantly cardiac or muscle involvement the Congo red test is negative and of no diagnostic help. Even in secondary amyloidosis the Congo red test is not always positive. Dahlin states that if 90 per cent of the Congo red has to disappear in order to be considered positive, none of his five cases was positive.

Amyloidosis of the kidneys is clinically indistinguishable from nephrosis. As a matter of fact, amyloidosis of the kidneys is nephrosis for all practical purposes, since the amyloid is deposited in the renal tubules. Pure lipoid nephrosis occurs mostly in childhood and, therefore, in every case of a classical picture of nephrosis in adults, the possibility of amyloidosis should be entertained.

In the older age group, nephrosis is usually a stage of glomerulonephritis, the so-called nephrotic stage of nephritis. Since amyloidosis of the kidneys can also affect the glomeruli and look similar to kidneys of chronic glomerulonephritis, the differential diagnosis between the nephrotic stage of nephritis and amyloidosis of the kidneys is likewise practically impossible. Amyloid disease of the kidneys resembling chronic glomerulonephritis has been described by Noble and Major.[10]

If the Congo red test is positive, the diagnosis is evident. Otherwise, short of a biopsy of the kidneys, there is no other means of confirming the diagnosis.

It is generally accepted that amyloidosis is related to disturbed metabolism of protein. Injection of foreign protein is followed by amyloidosis in experimental animals.[11,12] Likewise, hyperglobulinemia has been found in experimental amyloidosis.[13] It is known that hyperglobulinemia is due to high gamma globulin production by the mesenchymal cells and that injury of the connective tissue is associated with elevation of the gamma globulin. The high globulin is an antibody reaction in response to an antigen.[14]

A reversal of the A/G ratio in "primary" systemic amyloidosis of the heart is quite frequent.[5,15-17] Even in amyloidosis of the kidneys there is a reversal of the A/G ratio which is probably not due to renal disease, at least not in the

beginning, because the total protein is frequently normal.[4] Likewise, the urine in patients with renal amyloidosis frequently shows an increase in the protein fraction.[18]

That amyloidosis and para-amyloidosis are related to collagen diseases has been pointed out by Ehrich. Amyloidosis is probably due to perverted fibroblastic activity[9] or to an alteration of the mucopolysaccharide-reticulin response,[20] or to a reaction of the mucopolysaccharides with normal and more frequently abnormal protein.[14] Any stimulus can, in susceptible individuals, cause an irritation of the ground substance with resulting disease entity belonging to the hypersensitivity group which can be either one of the collagen diseases, amyloidosis or sarcoidosis. The ground substance consists of fibrils, mucopolysaccharides, and chondroitin sulfuric acid. In collagen disease and likewise in amyloidosis there is an increase of these substances. In both conditions there is also a hyperglobulinemia due to increased antibody production as a response to irritation of the ground substance. Amyloidosis following such diseases as rheumatic fever and rheumatoid arthritis has been reported.[21,22] This constitutes a further link in the hypothesis that there is a close relationship between amyloidosis and collagen disease.

An elevated globulin is classical in multiple myeloma and it is assumed[14] that the amyloidosis following multiple myeloma is due to the precipitation of normal or abnormal protein.

Apitz[23] goes even so far as to postulate that every case of primary amyloidosis is associated with plasma-cell proliferation and is either an unrecognized or a burned-out case of plasma-cell proliferation.

The following sequence of events can be postulated in amyloidosis: irritating stimulus, injury of the ground substance, increased protein production, precipitation of circulating protein into sensitized collagen tissue, and amyloid formation.

ACTH has been tried in multiple myeloma and in other conditions terminating in amyloidosis, such as ulcerative colitis, regional enteritis, rheumatic fever, and rheumatoid arthritis. The action of ACTH on the ground substance is well known. It seems to inhibit collagen formation and fibril production. It diminishes the permeability of the connective tissue and decreases antibody formation and plasma-cell and gamma-globulin production because of its catabolic effect. Since ACTH and cortisone are supposed to have a modifying action on the collagen tissue, they are therefore indicated in primary amyloidosis. ACTH is indicated in nephrosis.[24] Theoretically, ACTH is contraindicated in heart failure. However, ACTH has recently been advocated for treatment of idiopathic myocarditis (Fiedler's isolated myocarditis). Perhaps with progress in cardiac surgery it will be possible to perform biopsies in selected cases for diagnostic purposes. Cardiac surgery has been advocated recently for diagnostic purposes by Bailey and associates.[25] In heart failure due to amyloidosis of the heart, ACTH is probably the only hope for an improvement. It is known that amyloidosis, at least in the early stages, is a reversible process. Grayziehl and Jacobi[26] reported that after treatment of amyloidosis with dessicated-whole-liver

powder he observed reabsorption and disappearance of amyloid deposits. Likewise Waldenstrom[27] states that amyloid can disappear from the tissues in early stages.

SUMMARY AND CONCLUSIONS

1. Two cases of primary amyloidosis, one of the heart and one of the kidneys, are reported.

2. Primary amyloidosis is probably caused by an imbalance of the A/G ratio as a response to an irritative stimulus with deposition of protein into the sensitized ground substances.

3. Primary amyloidosis belongs to the group of hypersensitivity diseases.

4. Since it has been postulated that amyloidosis is caused by plasma-cell proliferation, present or past, a search for plasma cells should be made in every case of suspected amyloidosis. This can be helpful in establishing a diagnosis.

5. ACTH should be tried in every case of amyloidosis.

REFERENCES

1. Rokitansky, C.: Handbuch der Path. Anat., Vol. 3, Vienna, 1842, p. 331.
2. Virchow, R.: Ueber den Gang der Amyloiden Degeneration, Virchows Arch. f. path. Anat. **8**:364, 1855.
3. Wilks, S.: Cases of Lardaceous Disease and Some Allied Affections, Guy's Hosp. Rep. S. 3. **2**:103, 1856.
4. Dahlin, D. C.: Classification and General Aspects of Amyloidosis, M. Clin. North America **34**:1107, 1950.
5. Dahlin, D. C.: Primary Amyloidosis With Report of Six Cases, Am. J. Path. **25**:105, 1949.
6. Eisen, H. N.: Primary Systemic Amyloidosis, Am. J. Med. **1**:144, 1946.
7. Lindsay, S.: Primary Systemic Amyloidosis With Nephrosis, Am. J. Med. **4**:765, 1948.
8. Christian, H. A.: The Nephrotic Syndrome Associated With Idiopathic Amyloidosis, M. Clin. North America **15**:805, 1932.
9. Stauffer, M. H.: Hepatic Manifestations in Secondary Amyloidosis, M. Clin. North America **34**:1165, 1950.
10. Noble, J. F., and Major, S. G.: Renal Insufficiency in Amyloid Disease, Arch. Path. **8**:762, 1929.
11. Dick, G. F., and Leiter, L.: Some Factors in the Development, Localization and Reabsorption of Experimental Amyloidosis in the Rabbit, Am. J. Path. **17**:741, 1941.
12. Jaffe, R. H.: Amyloidosis Produced by Injection of Proteins, Arch. Path. **1**:25, 1926.
13. Eklund, C. M., and Reimann, H. A.: The Etiology of Amyloid Disease, With a Note on Experimental Renal Amyloidosis, Arch. Path. **21**:1, 1936.
14. Ehrich, W. E.: Nature of Collagen Diseases, Am. Heart J. **43**:121, 1952.
15. Couter, W. T., and Reicherd, R. E., Jr.: Primary Systemic Amyloidosis Mimicking Chronic Constrictive Pericardial Disease, Circulation **2**:441, 1950.
16. Lindsay, S.: The Heart in Primary Systemic Amyloidosis, Am. Heart J. **32**:429, 1946.
17. Findley, J. W., Jr., and Adams, W.: Primary Systemic Amyloidosis Simulating Constrictive Pericarditis, Arch. Int. Med. **81**:342, 1948.
18. Bell, E. T.: Renal Diseases, 1947, Philadelphia, Lea & Febiger, p. 225.
19. Mallory, F. B.: Principles of Pathologic Histology, Philadelphia, 1914, W. B. Saunders Company. (Reprinted in 1925.)
20. Jones, R. S., and Frazier, D. B.: Primary Cardiovascular Amyloidosis; Its Clinical Manifestations, Pathology and Histogenesis, Arch. Path. **50**:366, 1950.
21. Unger, P. N., Zuckerbrod, M., Beck, G. J., and Stelle, J. M.: Amyloidosis in Rheumatoid Arthritis; a Report of Ten Cases, Am. J. M. Sc. **216**:51, 1948.
22. Beattie, J. M.: Rheumatic Fever and Amyloid Degeneration, Brit. M. J. **2**:1444, 1906.
23. Apitz, K.: Quoted by Ehrich.[14]
24. Thorn, G. W., Forsham, P. H., Frawley, T. F., Hill, S. R., Jr., Roche, M., Staehelin, D., and Wilson, D. L.: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**:783, 824, 865, 1950.
25. Bailey, C. P., Glover, R. P., and O'Neill, T. J. E.: Exploratory Surgery of the Heart, Dis. of Chest **22**:640, 1952.
26. Grayziehl, H. G., and Jacobi, M.: Secondary Amyloidosis: Results of Therapy With Dessicated Whole Liver Powder, Ann. Int. Med. **12**:39, 1938.
27. Waldenstrom, H.: Ueber das Entstehen und Verschwinden des Amyloids beim Menschen Klin. Wchnschr. **6**:2235, 1927.

ABSENCE OF THE LEFT PULMONARY ARTERY

A Report of Six Cases with Autopsy Findings in Three

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INTRODUCTION

SINCE 1868, as far as can be determined, there have been ten recorded patients[1,2,4-6,10,12,13,16,17] with absence of one branch of the main pulmonary artery. All of these were diagnosed by autopsy or surgical operation. In 1952, Madoff and associates[11] added an eleventh case and their study, including angiocardiography and bronchospirometry, showed quite conclusively that the lesion in question was a congenital absence of the right pulmonary artery. This patient, a 14-year-old girl, was apparently the first reported patient in whom the diagnosis was made before autopsy or surgery. Their paper presented an excellent tabulation of the previous cases and dealt largely with the disturbed physiology of the pulmonary respiration and circulation associated with the anomaly.

Including the case reported by Madoff and associates there have been eight females, two males, and one with sex not recorded. In all except one patient there were minor or major cardiac anomalies. No anomalies of other systems were recorded. Four patients died of conditions unrelated to the anomaly, one at the age of thirty-five years from puerperal sepsis. It is apparent that the anomaly is compatible with survival and may be unsuspected in routine investigation.

Of the eleven cases reported, eight had absence of the right pulmonary artery and three had absence of the left pulmonary artery. The associated cardiac anomalies included one with aortic septal defect, three with patent ductus arteriosus, three with patent foramen ovale, one with multiple anomalies including coarctation of the aorta, one with tetralogy of Fallot, one with "pulmonic stenosis," and one with absence of the transverse aortic arch. In four instances, it was noted that the affected lung or hemithorax was smaller than the other side.

The three recorded examples of absent left pulmonary artery are of particular interest to us. The first one was a post-mortem examation by Thomas[17] of a 3-month-old female infant who died with tetralogy of Fallot. This infant had an anomalous vessel arising from the aorta, to the left of a left innominate

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artery and entering the left lung, and there was a right-sided aortic arch and absence of the ductus arteriosus.

The second case of absent left pulmonary artery was noted by Blalock[2] during an operation. The left lung received a branch from a left innominate artery and a right-sided aortic arch was noted.

The third example of absent left pulmonary artery was observed by Sweet and White[16] in a 28-year-old female from whom they removed the upper lobe of the left lung for a hemorrhage which had resulted from a ruptured atheromatous branch of an anomalous artery. This artery was a branch of the distal third of the aortic arch. It supplied the left lung with a copious amount of blood and exceeded the descending aorta in diameter. The authors state that "evidence of other cardiac anomalies" was present but, as the patient is still alive, the other anomalies are not known.

Humphreys[7] cites two cases of a somewhat different type of anomaly in which there was a true truncus arteriosus. One case was a male newborn infant with the left pulmonary artery originating from the truncus, absent right pulmonary artery and ductus, and the right lung supplied by two bronchial arteries. The other case was a 4-month-old male infant with a solitary right pulmonary artery from the truncus in whom the left lung was supplied by bronchial arteries.

The present paper deals with the history, investigation, clinical course, and autopsy findings in three patients with absence of the left pulmonary artery. This anomaly has been observed three times in a total of 210 hearts with congenital anomalies examined at autopsy at this hospital.

Three additional patients, presently living, in whom presumptive diagnoses of absence of the left pulmonary artery have been made, will be briefly considered. All patients have been under the care of the departments of cardiology and surgery of The Children's Memorial Hospital, Montreal.

CASE REPORTS

CASE 1.—D. C., a 5-year-old female, was admitted on Nov. 10, 1947, and died on Dec. 12, 1947. She was first noted to have cyanosis at age 7 months. Although there had always been marked limitation of activity, she had had no spells of unconsciousness. The mother's pregnancy and delivery were normal.

On examination, she was seen to be underdeveloped and moderately cyanotic about the lips and nails with clubbing of the fingers. Cardiac examination revealed a harsh, moderately loud, systolic murmur, maximal in the third left intercostal space, and transmitted into the posterior thorax and left axilla.

Oxygen saturation of the femoral artery blood was 75 per cent. The electrocardiogram showed a pattern of right ventricular hypertrophy. Plain films of the chest showed definitely less vascularization of the left lung as compared to the right, a slightly smaller left lung, slight shift of the mediastinum to the left, and slight crowding of the ribs on the left. Aeration of the left lung was normal. No anomalies of ribs or vertebrae were present.

On fluoroscopy, there was a right aortic arch, a small pulmonary artery, reduced hilar vascular markings, and a large right ventricle. Cardiac catheterization revealed a high right ventricular pressure, a reduced pulmonary artery flow, and a considerable right-to-left shunt.

In the angiocardiogram, the aorta and main pulmonary artery filled simultaneously, but there was no filling of the left pulmonary artery or its branches (Fig. 1). The clinical diagnosis was tetralogy of Fallot with right aortic arch and a small or absent left pulmonary artery. It

was decided to do an exploratory thoracotomy on the left side and, if a pulmonary artery was present, to perform an anastomosis.

At this operation, what appeared to be a small left pulmonary artery was found but the artery was not considered of adequate size for an anastomosis. The operative findings, therefore, indicated that it was safe to perform an anastomosis on the right in view of the presence of a left pulmonary artery. At the second operation, the right pulmonary artery was exposed to its bifurcation in the hilus of the right lung. An end-to-side anastomosis was accomplished between the right subclavian and the right pulmonary artery. The pulse and blood pressure fell shortly after clamping the right pulmonary artery. After completion of the anastomosis, the heart stopped and it was not possible to restore its activity.

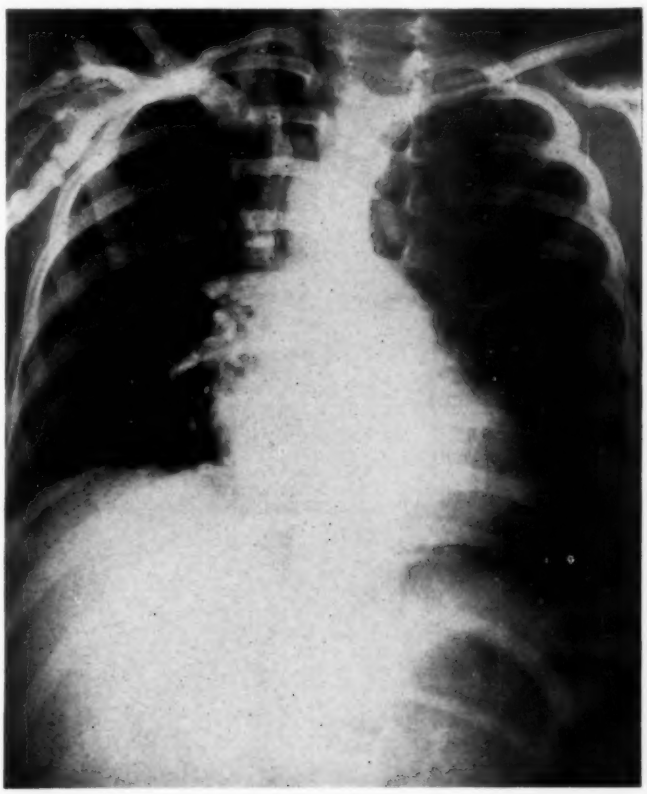


Fig. 1.—Case 1. Angiocardiogram. The left pulmonary vascular tree is not opacified by Diodrast, whereas the right pulmonary vessels fill normally.

CASE 2.—M. M., a 26-month-old female infant, was admitted on May 1, 1951, and died May 14, 1951. She had appeared normal until 9 months of age when a respiratory infection caused an episode of dyspnea, cyanosis, tremor, and stiffness of the limbs. She had had five admissions because of cyanosis and dyspnea, prior to her final admission. The pregnancy, delivery, and neonatal period were normal.

At 26 months of age, she weighed 16 pounds and there was moderate, generalized cyanosis and clubbing of fingers and toes. There was a loud systolic murmur heard maximally in the pulmonary area and associated with a slight thrill.

Oxygen saturation of the femoral artery blood was 62 per cent. The electrocardiogram showed right ventricular hypertrophy. On fluoroscopy, there was a right aortic arch, a small main pulmonary artery, reduced hilar vascular markings, and a large right ventricle. Plain films of the chest did not reveal a significant difference between the two lung fields.

The angiocardiogram showed a right aortic arch and simultaneous filling of the aorta and main pulmonary artery from the right ventricle. The main pulmonary artery appeared small and both intrapulmonary branches appeared to be filled. The clinical diagnosis was tetralogy of Fallot with right aortic arch.

At operation, a right aortic arch was seen and the right pulmonary artery was identified and dissected out. When it was occluded in order to perform the anastomosis, cardiac arrest occurred, and the patient died after a brief period of ventricular fibrillation.

CASE 3.—P. B., a 20-month-old male infant, was admitted on Aug. 2, 1952, and died on Aug. 31, 1952.

The infant had never thrived and a diagnosis of congenital heart disease was made at 5 months of age. He had a history of chronic respiratory infections, dyspnea, weakness, and loss of weight, and died in an episode of extreme cyanosis and dyspnea.

Fig. 2.—Case 1. Anterior view of heart, aorta, single right pulmonary artery (partially opened), and hilus of left lung. Note cordlike vessel (obliterated ductus) passing from left innominate artery to the hilus of the left lung where it becomes continuous with a wider patent vessel which gives off normally distributed intrapulmonary branches of a left pulmonary artery.

Cardiac assessment at the age of 19 months revealed a moderately loud systolic murmur, maximal in the third and fourth intercostal spaces along the left sternal border, and an unusual electrocardiogram, which could be interpreted as combined ventricular hypertrophy. Cardiac enlargement and a right aortic arch were present on the chest roentgenogram. Plain films of the chest showed moderate differences between the right and left side of the chest, as in Case 1. The right lung, however, showed unusually prominent vascular markings. The clinical diagnosis was chronic respiratory infection, malnutrition, and congenital heart disease, probably cyanotic type.

GROSS AUTOPSY FINDINGS

CASE 1.—

(1) *General findings:* Typical tetralogy of Fallot with stenosis of the pulmonary valve, bicuspid pulmonary valve, hypertrophy and dilatation of the right ventricle, high interventricular septal defect, and dextroposition of the aorta.

There was a slight shift of the mediastinum to the left. The lungs were mildy congested but otherwise were not remarkable. There was no recorded difference between the two lungs as to size. No collateral circulation to the left lung was noted. The remainder of the autopsy findings were irrelevant.

(2) *IV and VI arch derivatives:* The main pulmonary artery was continuous with the right pulmonary artery, curving upward, backward, and to the right, to end in normal hilar branches to the right lung. There was no left pulmonary artery nor was there a bulge or depression in the main pulmonary trunk to suggest the site of a left branch.

The aortic arch was on the right. The first branch of the aortic arch was the left innominate which immediately divided into three branches, the left common carotid, the left subclavian, and an anomalous vessel.

This anomalous artery entered the hilus of the left lung, where it divided into the normal and patent branches of a pulmonary artery (Fig. 2). It was 35 mm. in length, 2 mm. in external diameter at its origin, and 1 mm. in external diameter until it reached the left lung where its branches varied from 1 to 3 mm. in external diameter. The lumen of the vessel was obliterated in the central portion for a distance of 2 cm. Each end had a funnel-shaped lumen, the aortic end measuring 0.8 cm., and the pulmonary end 1.0 cm. in length.

The aortic arch also gave off, in subsequent order, the right common carotid and the right subclavian. The latter vessel had been anastomosed to the inferior branch of the right pulmonary artery. A probable tiny right ductus arteriosus connected the right pulmonary artery (3.4 cm. from the pulmonary valve) to the posterolateral aspect of the first part of the aortic arch (3.5 cm. from the aortic valve). This vessel measured 10 mm. long and 1 mm. in external diameter. No lumen could be seen grossly but, microscopically, a tiny lumen was present. The wall was highly muscular and showed no obliterative changes in the intima. In spite of its small size, we considered this to be a right ductus arteriosus.

CASE 2.—

(1) *General findings:* Typical tetralogy of Fallot with a bicuspid stenotic pulmonary valve, hypoplasia of the pulmonary conus, hypertrophy and dilatation of the right ventricle, high interventricular septal defect, and dextroposition of the aorta.

There was a slight shift of the mediastinum to the left. The left lung was pale pink in color and well aerated. The right lung was collapsed and congested. There was no recorded difference between the two lungs as to size. No collateral circulation to the left lung could be found grossly.

(2) *IV and VI arch derivatives:* The main pulmonary artery was continuous with the right pulmonary artery as seen in Case 1. The right pulmonary artery divided at the hilus into an inferior and a superior branch. The latter showed ties from the recent operation. There was no trace of a left pulmonary artery.

The ascending aorta, aortic arch, and descending aorta were on the right side. The first branch of the aortic arch was the left innominate which, as described in Case 1, divided into three branches, a left common carotid, a left subclavian, and an anomalous vessel which entered the hilus of the left lung. The anomalous vessel measured 40 mm. in length, 1.5 mm. externally near the aortic end, 1.5 mm. externally at the mid-point, and 4 mm. externally near its branches. The origin of the vessel was patent and funnel-shaped, narrowing to an obliterated lumen after 0.2 cm. The vessel again widened into a funnel-shaped patent lumen for 0.5 cm. before it branched into the patent arteries to the lung. Post-mortem injection of barium sulfate into the right and left intrapulmonary arteries was done. The pattern was the same on both sides, although the caliber was smaller on the left. This, however, may have been due to the crude technique used. The aortic arch gave off a right common carotid and a right subclavian. There was no trace of a right ductus arteriosus.

CASE 3.—

(1) *General findings:* So-called Eisenmenger complex including a high interventricular

septal defect, overriding aorta arching to the right, normal pulmonary conus and valve, hypertrophy and dilatation of the right ventricle, dilatation of the right atrium, slight hypertrophy and dilatation of the left ventricle.

There was a marked shift of the mediastinal septum to the left (2.5 cm.), and it was attached to the bony thorax. The right lung was slightly more voluminous than the left and was evidently more aerated than the left. On cut section, the arteries of the right lung were much more prominent than the left because of their large size and dilatation. Otherwise, the lungs showed grossly no noteworthy lesion.

(2) *IV and VI arch derivatives:* As in Cases 1 and 2, the main pulmonary artery was continuous with the right pulmonary artery with no trace of a left pulmonary artery. In this case, the pulmonary vessels were of normal or increased caliber in contrast to the two tetralogies where the vessels were smaller than normal.

Exactly as in Cases 1 and 2, there was a left innominate artery which divided into a left common carotid, a left subclavian and a cordlike anomalous vessel which entered the hilus of the left lung. This vessel was 35 mm. long and passed anterior to the trachea and left main bronchus to provide branches which followed the segmental bronchi into the left lung. The lumen was obliterated and the vessel narrow (1 to 2 mm.) for most of its length, although there was a small lumen for a short distance at both the innominate and hilar ends. The hilar and intrapulmonary branches were patent and of good caliber.

In this patient, there were three minor anomalous blood supplies to the surface of the left lung, a small branch of the left internal mammary artery to the lingula and the pectoral segment, and a large vessel from the abdominal aorta to the diaphragmatic surface of the basilar segments. Both entered the pleura of the left lung via fine cardiopleural and pleurodiaphragmatic adhesions. They could be seen coursing over the surface of the pleura and, in sections, could be seen in the septa of the lung. Their intrapulmonary connections were not demonstrated. It could not be decided whether the adhesions were congenital or acquired. Thirdly, a small branch of an intercostal artery passed to the posterior basal and apical segments of the lower lobe.

A right ductus arteriosus was present, passing from the right pulmonary artery to the distal part of the aortic arch. It measured 5 mm. long and 3 mm. wide. The lumen was closed, but the aortic and pulmonary ends could still be identified as small indentations of the intima.

In summary, there were two cases with tetralogy of Fallot and one with Eisenmenger complex. All three cases had a right aortic arch and a left innominate artery. All three had an obliterated vessel running from the innominate artery to the hilus of the left lung. One case had a closed right ductus arteriosus, one had no right ductus arteriosus, and one had a probable right ductus arteriosus. In each instance, the main pulmonary artery was continuous with the right pulmonary artery, and there was no trace of a left pulmonary artery. The intrapulmonary distribution of the branches of the anomalous vessel was identical with that of a normal left pulmonary artery.

In two cases, there was a slight, and in one case a marked, shift of the mediastinal septum to the left. The right lung was notably more voluminous than the left in Case 3. Grossly, in all three cases, the left lung had undergone normal development. It was noted that, in one case, three minor collateral arteries supplied the left lung. The vagus, with its recurrent branches, which might have added information to the embryologic interpretation, was not dissected in any of the three cases.

MICROSCOPIC FINDINGS

There were no structural differences between the right and left lungs. In the two cases of tetralogy, the vessels did not show any abnormality or structural differences but, in the case with the Eisenmenger complex, the pulmonary arterioles of the right lung only showed definite, but not marked, medial hypertrophy, indicating a state of hypertension in the right lung. The arterioles of the left lung were normal. This is further and unique evidence of the effect of hypertension on the lung vasculature. In the so-called Eisenmenger complex, the pulmonary arterial

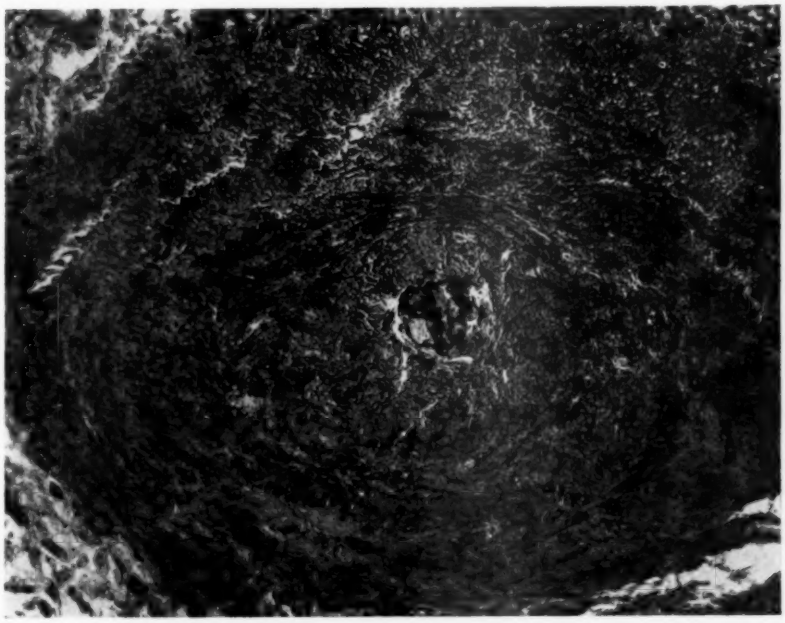


Fig. 3.—Cross section of anomalous vessel (obliterated ductus). Note small calcified mass centrally, with complete absence of lumen. Irregularly distributed smooth muscle fibers (fine, elongated, dark streaks) in media can be seen, particularly above the calcified mass. Mallory's phosphotungstic acid hematoxylin stain. (×110)

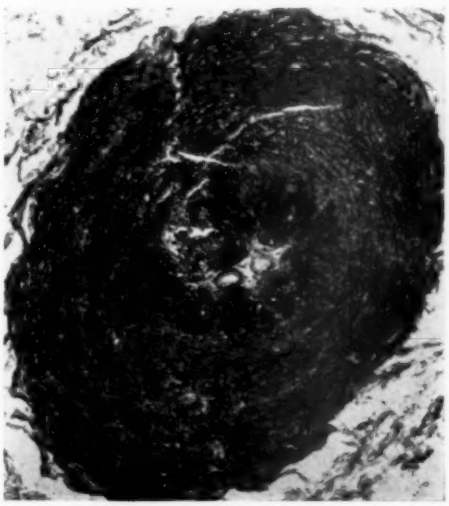


Fig. 4.—Cross section of obliterated ductus (anomalous vessel) showing fibro-elastic tissue filling the lumen and the wavy, black, intimal elastic lamina. Outside of this is a relatively wide, pale area with few elastic fibers (the muscular media). Peripherally, there is a considerable number of slightly fragmented elastic fibers, partly derived from the sleevelike extension of the pulmonary artery into the adventitia of the ductus. Weigert's elastic tissue stain. (×90)

pressure is of systemic levels but, in Case 3, the left lung was isolated from the main pulmonary circulation and thus hypertensive changes did not occur in its vessels.

Three blocks of tissue from each of the anomalous vessels were examined. These were taken from the aortic end, the mid-point, and the pulmonary end. Except for minor details, the structural appearance of the vessels from all three cases was similar.

The lumen of each vessel was obliterated at the aortic end and the mid-area. At several points tiny vascular channels were present which, on serial section, were found to disappear. The lumen was filled with a fibroelastic tissue of irregular pattern, at the outer edge of which could be seen remnants of the internal elastic lamina. In Cases 1 and 2, the tissue in the lumen presented a hyalinized appearance and scattered foci of calcified material were present.

Examination of the media in all instances showed the artery to be muscular (Fig. 3), as there were numerous smooth muscle fibers separated by fine fibrous tissue and scattered elastic fibers which tended to be more numerous near the junction with the adventitia (Fig. 4). These elastic fibers were moderately fragmented. Cases 1 and 2 showed more evidence of fibrosis of the media than the younger Case 3.

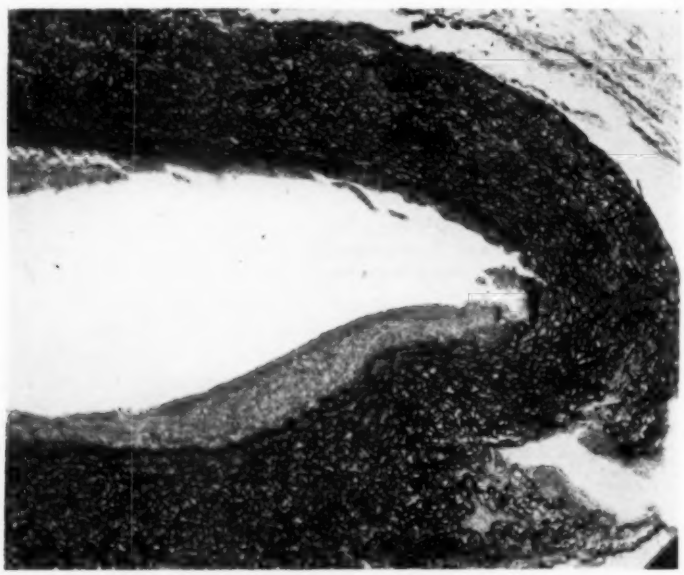


Fig. 5.—Cross section of patent pulmonary end of "anomalous vessel." Note predominant elastic character of media with its row on row of intact wavy black fibers. The patch of intimal thickening is an extension from the closed ductus. Weigert's elastic tissue stain. (×90)

The muscularity of the obliterated arteries contrasted with the predominant elastic character of the pulmonary end. As the vessels became patent at the hilus of the lung, the muscular constituents of the media disappeared and the media became essentially elastic with circularly arranged wavy fibers. At the lung end, each was an elastic artery similar to the normal pulmonary artery (Fig. 5).

It is evident from the muscular structure of the media, together with the noninflammatory obliterative changes in the intima, that this vessel is an obliterated left ductus arteriosus. This is confirmed by the fact that it is continuous with a highly elastic artery at the hilus of the left lung, which structurally is identical with a pulmonary artery.

CLINICAL CASES OF ABSENT LEFT PULMONARY ARTERY

In three living patients, a presumptive diagnosis of absence of the left pulmonary artery has been made and a summary of the findings to date is given.

CASE 4.—P. L., a 5-year-old girl with a history of cyanosis since 6 months of age, moderate limitation of activity due to shortness of breath, squatting, and retardation of growth. Exami-

nation revealed a split first sound, well heard second sound, and no murmur. The electrocardiogram was suggestive, but not typical, of right ventricular hypertrophy. Fluoroscopy showed prominence of the right ventricle, a small main pulmonary artery, and a large aorta arching to the left. There was a striking difference in the vascularity of the two lungs; it was markedly reduced on the left and normal or slightly increased on the right. Angiocardiogram showed instantaneous filling of the aorta and the right pulmonary artery from the right ventricle, but only a small amount of dye appeared in the left lung field in later films. On cardiac catheterization, the pressure in the right ventricle was of systemic level, and the aorta was easily entered, but the pulmonary artery could not be intubated. The diagnosis of tetralogy of Fallot with absent left pulmonary artery was made.

CASE 5.—E. A., a 5-year-old girl, cyanotic since birth with moderate limitation of activity and retardation of growth. On examination, a short, harsh, systolic murmur was noted in the pulmonic area, not associated with a thrill. In addition, there was a well-marked continuous murmur of "humming top" quality, heard over the right chest, maximally just below the clavicle. Electrocardiogram showed a pattern of right ventricular hypertrophy. On fluoroscopy, the heart was somewhat enlarged with a markedly uplifted apex and a very large aorta arching to the left. The vascularity of the right lung was about normal and significantly greater than that of the left. Angiocardiogram revealed immediate filling of the aorta from the right ventricle and simultaneous filling of the vessels of the right lung. An anomalous vessel was seen to arise in the region of the right innominate artery and to arch downward. There was some dye in the left lung field, but no definite main or left pulmonary artery was seen. On cardiac catheterization, as in Case 4, only the aorta was entered.

It is believed (Case 5) that the right lung receives blood through the anomalous vessel which, in view of its site of origin, probably represents a right ductus, and that this accounts for the continuous murmur. Although there is evidence of absence of the left pulmonary artery, the over-all picture is difficult of interpretation because the true right pulmonary artery cannot be demonstrated. In fact, the right pulmonary artery could be absent, with a patent right ductus supplying the right intrapulmonary branches and with a severely stenotic left pulmonary artery. This case is recorded to indicate the possible complexities resulting from malformation of the pulmonary arches. It is of note that, in both these cases, an overriding aorta and a reduced pulmonary flow are present, but the benefit of a shunting operation is in considerable doubt.

CASE 6.—L. W., a 5-year-old boy, was examined in infancy because of a history of episodes of cyanosis and the presence of a heart murmur requiring elucidation before adoption. An angiocardiogram was done which showed dye passing from the right ventricle into a normal-sized main pulmonary artery and thence into the right lung. There was no opacification of any pulmonary vessels in the left lung until dye, returning into the left side of the heart, had opacified the aorta, which had a normal course, arching to the left.

Examination at 4½ years of age showed a well-developed boy who was normally active and showed no trace of cyanosis. A harsh systolic murmur was present below the right clavicle with a faint systolic thrill palpable in the vessels of the neck. At times, a soft continuous murmur was thought to be present. The electrocardiogram showed a pattern of right ventricular hypertrophy. On fluoroscopy, the heart was not definitely enlarged but showed some prominence of the right ventricle. There was a significant difference in the vascularity of the two lungs; it was normal on the right and reduced on the left.

A definite diagnosis, beyond absence of the left pulmonary artery, has not been made in this case.

EMBRYOLOGY

The embryologic studies of Congdon[3] on the aortic arch system of human fetuses has been used as the major reference in the interpretation of the vascular anomalies present in these three cases.

For convenience, he has divided the transformation of the aortic arch system into two main contrasting phases: (1) branchial, and (2) postbranchial. The branchial phase marks the earliest period of development when the vessels approximate the pattern which in lower vertebrates follows the gill arches. The postbranchial phase is characterized by a change from branchial to adult type vessels, and its commencement is arbitrarily marked by the disruption of the pulmonary arch. The paired aortic arches develop in a period of five to six weeks, extending approximately from the third to the ninth fetal week.

The evidence of most workers shows that the aortic arches originate primarily from a pre-existing vascular network which receives a bud from the dorsal aorta and one from the primitive aortic sac. Before the formation of the pulmonary or VI arch, two vessels (primitive pulmonary arteries) passing from the aortic sac to the rudimentary pulmonary plexuses, are clearly present before the bud from the aortic end appears. The bud from each dorsal aortic arch grows out to join the respective primitive pulmonary artery at a right angle, thus completing the pulmonary arch. This aortic component on the left is the ductus arteriosus of the full term fetus. On the right side, it normally disappears at the end of the branchial phase of development. Huntingdon[8] has found a similar formation of the VI arch in cats and albino rats. He has also observed that the primitive pulmonary plexus is joined by branches of the dorsal aorta so that, when the primitive pulmonary artery grows into the plexus, there is already a communication between pulmonary and systemic circulations. Congdon was unable to confirm this connection between the pulmonary plexus and dorsal aorta in human fetuses.

In view of the controversy concerning the existence of a fifth aortic arch and the complete absence of any rudiment beyond the earliest fetal life, it has not been considered as a possible cause of the anomaly.

The first and second paired arches quickly disappear. The third paired arch becomes the right and left common carotid arteries. The fourth arch on the right becomes the right innominate artery and, on the left, the aortic arch.

The postbranchial phase (Fig. 6) is marked by the interruption of the three remaining paired arches in four regions, the segment of each dorsal aorta between the third and fourth arches, the segment of the right dorsal aorta between the subclavian artery and the unpaired dorsal aorta, and the part of the right pulmonary arch between the aorta and the primitive right pulmonary artery. These vascular segments disappear without trace except for the pulmonary arch. The broken right pulmonary arch behaves uniquely by remaining for a time as a long cord of degenerating cells (Congdon). It is evident that the aortic component of the pulmonary arch is intrinsically different from the remainder of the aortic arch system.

The earliest sign of the development of the two primitive pulmonary arteries (Fig. 7) was noted by Congdon[3] after the completion of the fourth aortic arch and the presence of a lung bud with differentiated primary lobes. The VI arch on each side is formed when the caudally-growing primitive pulmonary artery is tapped by a bud from the dorsal aorta, dividing the primitive pulmonary artery into a proximal heart-end and a distal lung-end. The heart-end, together

with the component from the dorsal aorta, becomes the pulmonary arch. The next change of embryologic importance is the interruption of the right pulmonary arch by loss of the aortic component, as previously described. The two pulmonary arteries, which, up to now, have been separated by the length of the pulmonary component to the left pulmonary arch, gradually move together to assume the adjacent origins which are seen in the adult as the bifurcation of the main pulmonary artery. In the meantime, the aortic trunk has undergone the well-known spiral division to produce the separate pulmonary trunk known as the main pulmonary artery.

The IV arch derivatives in these three cases represent a right-left reversal. The right dorsal aorta has remained as a right descending aorta with the right IV arch forming the permanent right aortic arch. The left IV arch has formed the left innominate artery which is the counterpart of the aortic arch.

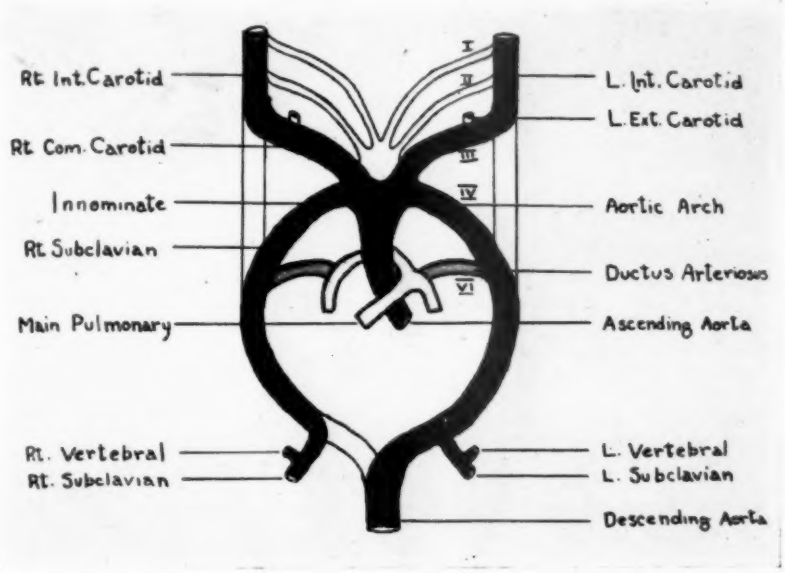
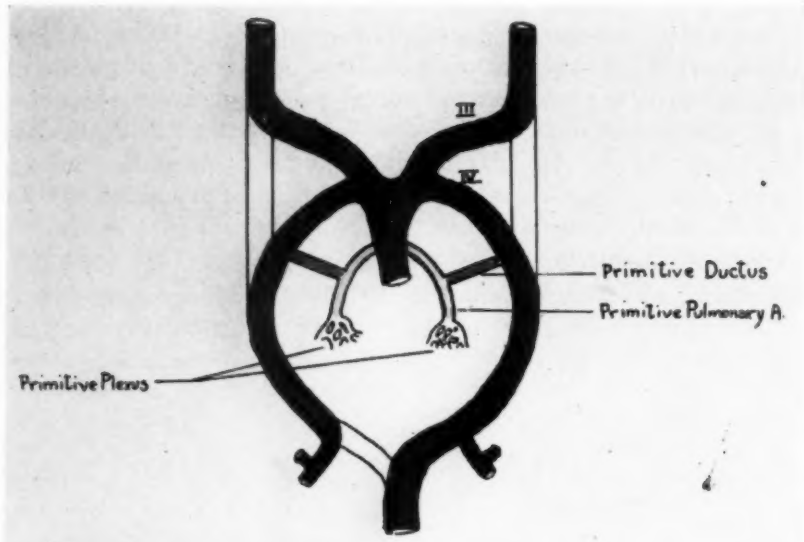


Fig. 6.—Development of aortic arches. Human fetus (adapted from Congdon[3]).

There are two possibilities as to the fate of the left pulmonary artery in our cases (Fig. 8). Possibly, it united normally with the primitive pulmonary vascular plexus and the heart-end disappeared after being joined by the bud from the dorsal aorta, leaving the aortic bud continuous with the pulmonary end of the primitive pulmonary artery. On the other hand, the left primitive pulmonary artery may have failed to develop and the aortic bud grew directly into the pulmonary plexus to become the source of blood supply to the growing lung. The perfect anatomic development of the hilar and intrapulmonary arteries slightly favors the original development of a left primitive pulmonary artery and the subsequent involution of that portion proximal to the union with the aortic bud, but of this there is no proof.

Fig. 7.



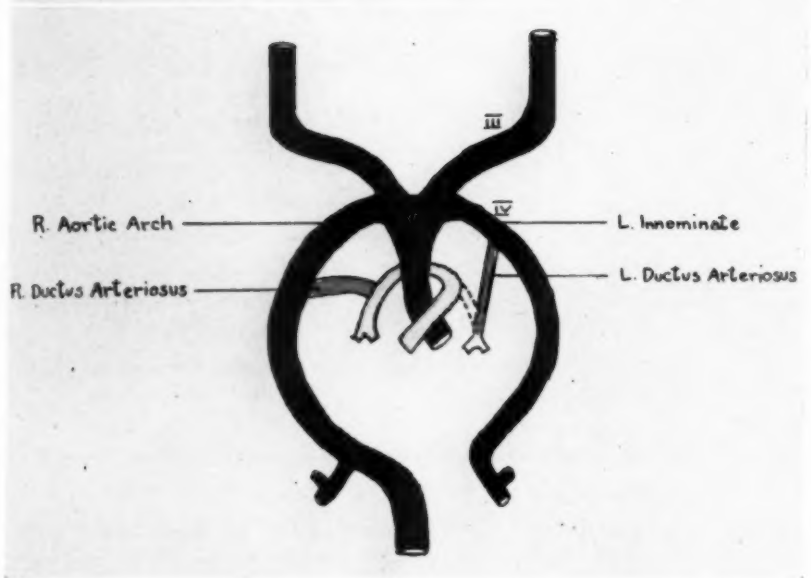


Fig. 8.

Fig. 7.—Pulmonary arches. Primitive pulmonary arteries arising from aortic sac and proceeding to lung buds. They are joined by a bud from the dorsal aortae.

Fig. 8.—Anomaly. The broken line indicates the absent "heart-end" portion of the left pulmonary artery in the autopsy cases. The left ductus arises from the persistent left aortic root as represented by the left innominate artery. The right obliterated ductus was also present in Case 3.

DISCUSSION

The anomalous vessel, from the innominate artery to the hilus of the left lung, found in our three cases at post mortem has been shown to be an obliterated left ductus arteriosus. Embryologically, it is evident that the ductus arteriosus can arise from the innominate artery, and this is confirmed by the occasional finding at autopsy of a ductus arteriosus uniting a normally formed pulmonary artery with the innominate artery. Therefore, the site of origin is perfectly compatible with that of a ductus arteriosus.

Neither is the presence of bilateral ductus arteriosi, as in two of our cases, an impossibility. Bilateral ductus have been reported by Peacock,[13] Salzer,[14] and Kelsey and associates,[18] and, very recently, we have examined at post mortem a case of tricuspid atresia with complete transposition of the great vessels, in which there were bilateral ductus arteriosi in their normal relationship. This being so, the cases of absence of one or other pulmonary artery, reported by Frantzel,[6] Döring,[4] Ambrus,[1] and Jew and Gross,[10] have had bilateral ductus arteriosi. Furthermore, there may be a single right ductus or complete absence of a ductus.

Grossly and microscopically, it is obliterated over the greater part of its course and the obliterative changes are similar to those described by Jager and Wollenman.[9] Above all, it has been shown to be a muscular artery, connecting two elastic arterial systems. At its pulmonary end, where the lumen is patent, the wall is identical with the elastic wall of a pulmonary artery. The fact that it is so frequently obliterated is in itself evidence that it was originally a ductus arteriosus. Then, too, the left lung is normally developed and of practically normal size. It might be postulated that the normal size of the left lung at birth is at least partly dependent on a sufficient volume of blood reaching the lung through this ductus. With closure of this ductus, the volume of blood entering the lung is reduced markedly, a process which may in part account for the smaller size of the lung as compared to the contra-lateral organ.

It is most important to point out that, as in the case of patency of a normally situated left ductus, the ductus, in these cases of absent right or left pulmonary artery, may remain patent. This is illustrated by Blalock's case[2] of a functioning vessel from the left innominate artery ". . . supplying most of the blood to the lung," those reported by others,[1,6,10,15] as well as possibly by Case 5 of our living series.

The reverse relationship to the aortic arch should be again stressed. In all cases where the aortic arch was observed, it was on the side opposite to the absent pulmonary artery. However, it is not possible to be dogmatic about this point for, in Cases 4 and 6 and possibly Case 5 of our living group, the absent left pulmonary artery appears to be associated with a left aortic arch.

Sex difference, on statistical analysis of the sixteen cases in which the sex is recorded (twelve females and four males), is of doubtful significance, being at the 5 per cent level (a 1 in 36 possibility of occurring by chance). The series is at present too small for any definite conclusion.

The *diagnosis* of an absent right or left pulmonary artery may be first suggested by changes noted in the routine plain films of the chest. The hemithorax of the affected side may be seen to be smaller and the ribs more closely spaced, with slight shift of the mediastinal septum. The affected lung may appear undervascularized as compared to the opposite lung. Nevertheless, it must be pointed out that, in complicated cardiac anomalies, particularly with pulmonary stenosis, one lung may be undervascularized as compared to the other because of an unequal distribution of a collateral circulation, even though both right and left pulmonary arteries are present.

Angiocardiography is the most valuable method of examination but, as seen in Case 2 of our autopsy series, this technique may fail to demonstrate the abnormality, presumably associated with an adequate collateral circulation. Furthermore, patency of the unusually situated ductus arteriosus may confuse the issue. Differential oxygen consumption between the two lungs is probably very significant but the performance of such an estimation is dependent on the age of the patient and availability of the apparatus.

The *physiologic significance* of this anomaly is that the lung, deprived of its pulmonary circulation, does not participate in oxygen exchange. In the case studied by Madoff and associates,[11] the affected lung was responsible for only 6 per cent of the oxygen uptake, although it handled 37 per cent of the inspired air. Thus, when the single pulmonary artery is clamped or cut off, the patient is immediately deprived of oxygen, unless an adequate collateral bronchopulmonary anastomosis has developed. The patient with one pulmonary artery absent is dependent on one lung for oxygenation, but the anomaly is compatible with life and may be asymptomatic.

From a surgical standpoint, it would be prudent, when contemplating an aorticopulmonary anastomosis or a pulmonary resection, to be reasonably certain that there is a pulmonary artery both on the operative as well as on the nonoperative side.

SUMMARY

Three cases have been presented in which an absent left pulmonary artery was demonstrated at post-mortem examination. The findings in three living patients, presumed to have an absent left pulmonary artery, are also briefly reported. The literature has been reviewed, and eleven cases of absent right or left pulmonary artery briefly commented upon.

1. The principal anatomic features are as follows:

   (a) Absence of the central or heart-end of the left pulmonary artery with persistence of a normal intrapulmonary portion. This anomaly has been associated with a variety of cardiac malformations. Both in our own series and those in the literature, there is a high incidence of an aortic arch on the side opposite to the absent pulmonary artery. However, at least two of our living cases show the arch and the apparently absent artery on the same side.

(b) An anomalous obliterated vessel running from the left innominate artery to the hilus of the left lung, continuous with patent, normally distributed, elastic intrapulmonary arteries. Evidence has been presented to show that the closed part of the vessel is an obliterated left ductus arteriosus. Almost certainly, the ductus portion may, on occasion, remain patent, as judged from the cases in the literature, whether there is an absent right or left pulmonary artery.

(c) A normally developed but small left lung, the size possibly secondary in part to the decreased blood flow.

2. The embryologic aspects of the anomaly have been discussed.

3. The physiologic and diagnostic aspects of absence of one or other branch of the pulmonary artery have been discussed and the importance of such absence in surgical operations involving occlusion of one branch of the pulmonary artery was emphasized.

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REFERENCES

1. Ambrus, G.: Congenital Absence of Right Pulmonary Artery With Bleeding Into Right Lung, J. Tech. Methods **15**:103, 1936.
2. Blalock, A.: The Technique of Creation of Artificial Ductus Arteriosus in the Treatment of Pulmonic Stenosis, J. Thoracic Surg. **16**:244, 1947.
3. Congdon, E. D.: Transformation of the Aortic-arch System During the Development of the Human Embryo, Carnegie Contrib. Embryol. **14**:47, 1922.
4. Döring, H.: Angeborener Defekt der rechten Lungenarterie. Studien zur Pathologie der Entwicklung. **2**:41, 1914. (Verlag, Gustav Fischer, Jena.)
5. Findlay, C. W., Jr., and Maier, H. C.: Anomalies of Pulmonary Vessels and Their Surgical Significance With Review of Literature, Surgery **29**:604, 1951.
6. Fräntzel, O.: Angeborener Defekt der rechten Lungenarterie, Virchow. Arch. f. Path. Anat. **43**:420, 1868.
7. Humphreys, E. M.: Truncus Arteriosus Communis Persistens, Arch. Path. **14**:671, 1932.
8. Huntingdon, G. S.: The Morphology of the Pulmonary Artery in the Mammalia, Anat. Rec. **17**:165, 1919-20.
9. Jager, B. V., and Wollenman, O. J., Jr.: An Anatomical Study of the Closure of the Ductus Arteriosus, Am. J. Path. **18**:595, 1942.
10. Jew, E. W., Jr., and Gross, Paul: Aortic Origin of the Right Pulmonary Artery and Absence of the Transverse Aortic Arch, Arch. Path. **53**:191, 1952.
11. Madoff, I. M., Gaensler, E. A., and Strieder, J. W.: Congenital Absence of the Right Pulmonary Artery, New England J. Med. **247**:149, 1952.
12. Miller, J. F.: Congenital Absence of Right Pulmonary Artery in Newborn Infant, With Resulting Necrosis of Lung and Spontaneous Pneumothorax, Am. J. Dis. Child. **53**:1268, 1937.
13. Müller, L.: Ueber angeborene Atresie der rechten Pulmonalarterie bei einem Erwachsenen (Beitrag zur Kenntnis des Kollateralkreislaufs der Lunge), Ztschr. f. Kreislaufforsch. **19**:561, 1927.
14. Peacock, T. B.: On Malformations of the Human Heart, ed. 2, London, 1866, Churchill, Case 16, p. 123-129.
15. Salzer, G.: Ueber einen Fall von Doppelseitigem Ductus Botalli, Beitrag. z. path. Anat. u. z. allg. Path. **81**:671, 1928-29.
16. Sweet, R. H., and White, P. D.: Quoted by Findlay, C. W., Jr., and Maier, H. C.: Anomalies of Pulmonary Vessels and Their Surgical Significance With Review of Literature, Surgery **29**:604, 1951.
17. Thomas, H. W.: Congenital Cardiac Malformations, J. Tech. Methods **21**:58, 1941.
18. Kelsey, J. R., Jr., Gilmore, Clarence E., and Edwards, J. E.: Bilateral Ductus Arteriosus Representing Persistence of Each Sixth Aortic Arch, Arch. Path. **55**:154, 1953.

THE CARDIOVASCULAR ASPECTS OF THE LOS ANGELES COUNTY MASS CHEST X-RAY SURVEY

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IT IS accepted generally that the mass chest x-ray survey is a valuable case-finding method for tuberculosis. However, there is considerable divergence of opinion as to its value in the detection of cardiovascular disease.[1-7] When a chest x-ray survey of Los Angeles County, the largest ever attempted in the United States, was to be conducted during 1950, it was realized that an unusual opportunity presented itself to study this problem. As a result the Los Angeles Heart Association appointed a committee to devise a program for the proper disposition and follow-up of those persons with abnormal cardiac silhouettes. The Chronic Disease Bureau of the California State Department of Public Health granted $40,000 to the Los Angeles Heart Association with the understanding that it was to:

". . . Establish and maintain an adequate system of follow-up of a maximum of 25,000 persons who, as a result of findings in the Los Angeles County X-ray Survey, are suspected of having heart disease.

". . . To include within the follow-up system, procedures for the recall and interviewing of heart disease suspects; for the rechecking of suspected films by experts; for the referral of suspects to appropriate sources of medical care for definitive diagnostic study; and for the maintenance of follow-up records to determine whether they reach the appropriate physician or clinic to receive cardiac care which is indicated."

In order to effect this program a cardiac retake center was established which for reasons of economy and convenience was integrated with the X-ray Survey Foundation's retake center. Four public health nurses, four clerks, and a technician were employed to staff this center and were responsible for the recalling and interviewing of all persons whose original films indicated possible cardiovascular abnormalities. The original 70 mm. films taken by the mobile x-ray units were interpreted by the United States Public Health Service physicians. Those persons thought to have an abnormal cardiac silhouette were requested to return to the retake center for a second 70 mm. film. These films were segregated for the convenience of the cardiac review boards. Sufficient funds were not available for conventional 14 x 17-inch films, nor was it felt that these were absolutely necessary for proper evaluation.

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In the retake center a short, pertinent cardiac history was obtained by a public health nurse prior to the taking of the second 70 mm. film. An attempt was made to secure the name of the person's private physician to whom a report of any abnormalities found on the confirmatory film might be sent and from whom a final diagnostic report might be obtained. All persons who did not come to the retake center in response to the first appointment letter were sent two additional follow-up letters, and finally, if possible, were contacted by telephone by one of the nurses. Of the 2,367 persons who did not report for second films, 1,119, or approximately 47 per cent, had already sought private medical care, and 0.013 per cent had died. The remaining 52 per cent (1,217 persons) could not be interested in further x-ray study for various reasons.

Under the supervision of William Paul Thompson, M.D., the confirmatory 70 mm. films were interpreted by teams of experts, consisting of one cardiologist and one radiologist, which met three times a week. Approximately fifty qualified specialists participated in this portion of the program. The diagnostic criteria for interpretation were the same as those established by the United States Public Health Service: (1) definite abnormalities of cardiac size; (2) definite abnormalities of cardiac contour; and (3) definite abnormalities of the great vessels. No attempt was made to postulate an etiologic diagnosis from the minifilm.

Those patients whose confirmatory films indicated the advisability of further study were referred directly to their private physicians or, lacking such, were notified to contact the Social Service Department either by telephone or in person. This department was composed of a stenographer, clerk, and two paid full-time and three volunteer part-time medical social workers. The following services were provided:

1. Referral to private physicians from a list provided and approved by the Los Angeles Heart Association.
2. Referral to a clinic if the person's financial situation so necessitated.
3. Consultation for persons coming to the retake center who expressed fear or concern regarding the suspected heart disease, or who had some other social or emotional problem which prevented their securing further medical care.
4. Referral to an appropriate social agency for additional casework service when indicated.
5. Referral of patients to social agencies or clinics at the request of private physicians.
6. Follow-up of all cardiovascular suspects to determine whether they received further study as indicated and to secure final diagnostic reports from physicians and clinics.

While the greater proportion of referrals for medical care (private physician, and free and part-pay clinics) was effected as a result of office interviews, a substantial number were made by telephone. Disposition of patients responding to their first letter of notification was completed as promptly as possible and in general the only follow-up required in these cases was to make certain that the diagnostic report pertaining to each was returned to the cardiac retake center. The percentage of follow-through among this group, as compared to the group not responding to the first letter, was not determined.

Originally, those persons who did not report to the Social Service Department within one month after the routine letter of notification had been sent were contacted by telephone, home call, or personal letter by one of the medical social workers who offered to assist with the arrangement for further medical

examination. Because of the rapid increase in volume of these follow-ups, it became necessary to devise another procedure. Therefore, double-fold post cards, mimeographed and numbered serially so that the patient could be identified without his signature, were sent with the request that one-half of the card be checked appropriately and returned. When completed, these cards provided information as to whether patients had already secured medical care, or whether they wished help in arranging such care, and the name and address of the physician or clinic. A total of 2,687 of these post cards was mailed and 1,629 were returned. Additional follow-up efforts included 1,693 letters and 641 telephone calls to patients, and 1,609 letters and 722 telephone calls to doctors requesting diagnostic reports. In the final analysis, 881 patients were never satisfactorily contacted, and in addition 1,214 final diagnostic reports from physicians were not received.

In addition to these patient services, the Social Service Department kept all the files and records and submitted monthly reports in coordination with those made by the records consultant for the Survey as a whole. Coding of all statistical material was done in this department with the close cooperation and guidance of a public health analyst from the Chronic Disease Bureau of the State Health Department.

Before presenting the statistical material obtained as a result of this cardiovascular program, it seems worthwhile to comment on some of the difficulties and problems encountered. Basically, all of these problems arose from a lack of sufficient planning as to what information was wanted from the Survey and how best to obtain it. This resulted largely from the swiftness with which the program was put into operation and, to some degree at least, probably was inherent in a mass survey where many groups in a community were asked to work together in a relatively short-term program. Specific difficulties arose from: (1) inconsistent interpretation of certain questions on the original cardiac history, particularly those pertaining to the patient's current status of medical care and previous history concerning heart disease; (2) insufficient records at the onset of the Survey pertaining to cardiac follow-up; (3) poorly devised final diagnostic report form and inadequate instruction to the physician asked to fill it out.

RESULTS

A total of 1,736,703 satisfactory 70 mm. films were taken during the Los Angeles County Mass Survey (Table I). Of these 67,966 (38.7 per 1,000) showed

TABLE I. CARDIOVASCULAR SUSPECTS ON FIRST SCREENING OF 70 MM. PHOTOFLUOROGRAPHIC FILMS

	NO.	RATE PER 1,000
Total 70 mm. survey films taken	1,755,001	
Total technically unsatisfactory	18,298	10.4
Total satisfactory 70 mm. films	1,736,703	989.6
Total essentially negative	1,668,737	950.8
Total abnormal films	67,966	38.7
Total cardiovascular suspects	10,899	6.3

abnormal findings. There was a total of 10,899 (6.3 per 1,000) that were considered suspicious of cardiovascular disease. Most of these had cardiovascular abnormalities only; others had tuberculosis, neoplasm, or other chest diseases as a primary screening impression in addition to evidence of cardiovascular disease (Table II).

TABLE II. DIAGNOSTIC CATEGORIES COMPRISING CARDIOVASCULAR SUSPECTS*

CATEGORY OF FINDINGS	NO.	RATE PER 1,000
Cardiovascular only	10,303	5.9
Tuberculosis and cardiovascular	201	0.1
Neoplasm and cardiovascular	167	0.1
Other chest disease and cardiovascular	228	0.1
Total	10,899	6.3

*These are the primary screening film impressions from which the cardiovascular suspects were obtained.

The race distribution of the cardiovascular suspects was: white, 5.9 per 1,000; Negro, 13.8 per 1,000; Latin American, 6.0 per 1,000 (Table III). Thus the incidence of cardiovascular suspects was twice as great among the Negroes as in other racial groups. A similar finding was reported by Rutstein and his group.[7]

TABLE III. RACE OF CARDIOVASCULAR SUSPECTS

RACE	NO.	RATE PER 1,000
White	9,066	5.9
Negro	1,180	13.8
Latin American	543	6.0
Oriental	90	7.1
Other	8	
Unknown	12	
Total	10,899	6.3

In the total survey population there were 47.9 per cent males and 52.1 per cent females. Among the cardiovascular suspects there were almost twice as many females (7.8 per 1,000) as males (4.6 per 1,000, Table IV). The distribution of the cardiovascular suspects by age and sex is shown in Table V and Fig. 1.

TABLE IV. SEX OF CARDIOVASCULAR SUSPECTS

SEX	NO.	RATE PER 1,000
Male	3,790	4.6
Female	7,109	7.8
Total	10,899	6.3

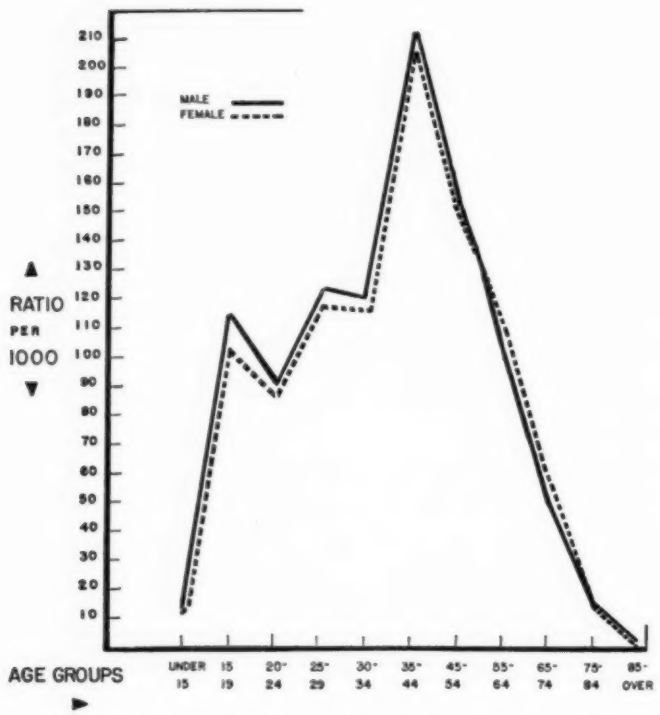

Fig. 1A.—Distribution of total x-rays taken by age and sex.

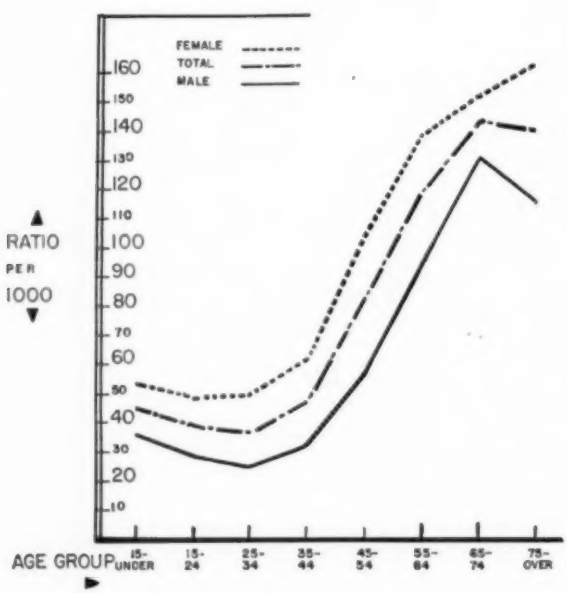

Fig. 1B.—Cardiovascular suspects by age and sex.

TABLE V. CARDIOVASCULAR SUSPECTS BY AGE AND SEX

AGE GROUP	BOTH SEXES		MALE		FEMALE	
	NO.	RATE PER 1,000	NO.	RATE PER 1,000	NO.	RATE PER 1,000
Under 15	115	4.5	41	3.6	74	5.3
15–24	1,323	3.9	463	2.8	860	4.9
25–34	1,541	3.7	492	2.5	1,049	4.9
35–44	1,710	4.7	541	3.1	1,169	6.1
45–54	2,221	8.2	722	5.7	1,499	10.4
55–64	2,190	11.9	800	9.7	1,390	13.8
65–74	1,393	14.2	570	13.0	823	15.2
75 and over	388	14.0	154	11.5	234	16.3
Unknown	18	3.7	7	3.0	11	4.3
Total	10,899	6.3	3,790	4.6	7,109	7.8

All the cardiovascular suspects were recalled to the retake center for a confirmatory 70 mm. film; 8,532 (78.3 per cent) returned, and 2,367 (21.7 per cent) did not return for this examination (Table VI). There was no difference in the percentage of males and females returning for confirmatory films. A definite diagnosis of heart disease was obtained in 113 (1 per cent) individuals who went directly to their private physician. It was learned that an additional 1,006 (9.2 per cent) were under medical care but no diagnoses were given by the physicians. Thirty-one patients died before a confirmatory film could be obtained. No information could be obtained concerning the remaining 1,217 (11.2 per cent) individuals.

TABLE VI. RESPONSE TO REQUEST FOR CONFIRMATORY 70 MM. FILM

RESPONSE	NO.			(%)		
Returned for confirmatory film	8,532			78.3		
Male		2,926			77.2	
Female		5,606			78.9	
Did not return for confirmatory film	2,367			21.7		
Male		864			22.8	
Female		1,503			21.1	
Diagnosis of heart disease obtained from physician			113			1.0
No diagnosis of heart disease obtained, patient under care			1,006			9.2
No diagnosis obtained, not known whether patient under care			1,217			11.2
Died before confirmatory film obtained			31			0.013
Total	10,899			100.0		

The confirmatory films were reviewed by groups of experts who found that 1,853 (21.7 per cent) showed no significant cardiac abnormality. This included 128 individuals with dextrocardia (Table VII). Of those individuals having positive film findings, 95.1 per cent had evidence of cardiovascular disease alone, and 4.3 per cent had evidence of cardiovascular disease associated with other significant abnormalities (Table VIII).

TABLE VII. DIAGNOSTIC IMPRESSIONS OF CONFIRMATORY FILMS OF CARDIAC SUSPECTS

	NO.	(%)
Essentially negative	1,853	21.7
Dextrocardia and other conditions not significant for follow-up	128	1.5
Abnormal, significant for follow-up	6,551	76.8
Total	8,532	100.0

TABLE VIII. SUMMARY OF CONFIRMATORY FILM IMPRESSIONS

	NO.	CONFIRMATORY IMPRESSIONS (%)	POSITIVE CONFIRMATORY IMPRESSIONS (%)
No cardiovascular abnormality	1,981†	23.2	
Positive confirmatory film impressions	6,551	76.8	100.0
Cardiovascular only	6,226		95.1
Cardiovascular and neoplasm	56		0.9
Cardiovascular and tuberculosis	46		0.7
Cardiovascular and other	173		2.6
Other combinations of above	9		0.1
Other findings*	41		0.6
Total	8,532	100.0	

*Neoplasm, tuberculosis or other chest pathology findings without cardiovascular abnormality mentioned.

†Includes 128 dextrocardias.

Table IX lists the type of medical practitioner or the agency to which the persons with positive confirmatory films were referred. At the onset of the survey anxiety was expressed that the cardiovascular program might place a burden on the medical facilities of the community welfare agencies. Therefore it is of considerable interest that 90.8 per cent of the referrals were made either to a private practitioner or a private hospital. There were 881 individuals (14 per cent) who could not be contacted for referral. It was possible to obtain 4,456 final reports (78.6 per cent) from physicians out of a total of 5,670 referrals. The distribution of the sources of the final reports was not significantly different from that of the referrals (Table X). These reports substantiated the confirmatory 70 mm. film as to the presence of cardiovascular disease in 3,388 instances (76.2 per cent, Table XI).

TABLE IX. TYPE OF MEDICAL PRACTITIONER OR AGENCY TO WHICH PATIENT WAS REFERRED*

TYPE OF PRACTITIONER OR AGENCY	NO.	(%)
Private physician, M.D.	3,838	67.7
Private physician, D.O.	559	9.9
Private physician, D.C.	76	1.3
Private practitioner, other	11	0.2
Private practitioner, unknown	243	4.3
Health department clinic	53	0.9
County hospital or clinic	337	5.9
Military hospital or clinic	41	0.7
Private hospital or clinic	380	6.7
Other	106	1.9
Unknown	26	0.5
Total—referrals made	5,670	100.0
No referral made	881	
Total	6,551	

*Patient referred to physician of his or her own choice.

TABLE X. SOURCE OF FINAL REPORT

SOURCE OF FINAL REPORT	NO.	(%)
Private physician, M.D.	3,203	71.9
Private physician, D.O.	467	10.5
Private physician, D.C.	60	1.4
Private practitioner, other	2	0.1
Private practitioner, unknown	99	2.2
Health department clinic	38	0.8
County hospital or clinic	192	4.3
Military hospital or clinic	32	0.7
Private hospital or clinic	250	5.6
Other	53	1.2
Death certificate	10	0.2
Unknown	50	1.1
Total—reports received	4,456	100.0
No report received	2,208	
No referral made	881	
Referral made	1,327	
Total	6,664*	

*Includes 113 persons who did not report for a confirmatory film, but for whom a final diagnosis was obtained.

TABLE XI. CONFIRMATION OF CARDIOVASCULAR DISEASE BY PHYSICIANS' DIAGNOSTIC REPORTS

	NO.	(%)
Total final reports received	4,456	100.0
Reports in which heart disease was confirmed	3,388	76.2
Reports in which heart disease was not confirmed	1,068	23.8

The etiology of the confirmed heart disease with age and sex distribution is shown in Tables XII and XIII, and Fig. 2. As might have been anticipated the etiologic distribution of confirmed heart diseases approximates that reported in other surveys. It is known that rheumatic heart disease occurs two to three times more often in females than in males. A similar incidence was noted in the present survey. However, in spite of the fact that arteriosclerotic heart disease occurs much more frequently in males than females, the incidence of this disease in this survey was the same in both sexes. As in the cardiovascular suspects, there were almost twice as many females (2.4 per 1,000) with heart disease confirmed by physicians' reports as males (1.5 per 1,000), and in both groups the sex

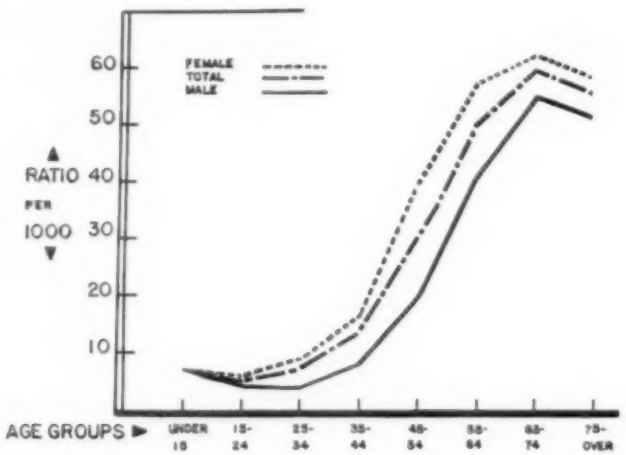

Fig. 2.—Confirmed heart disease by age and sex.

TABLE XII. ETIOLOGY OF CARDIOVASCULAR DISEASE FROM PHYSICIANS' REPORTS*

	NO.	RATE PER 1,000	MALE		FEMALE	
			NO.	RATE PER 1,000	NO.	RATE PER 1,000
Arteriosclerotic	881	0.5	399	0.5	482	0.5
Rheumatic	1,022	0.6	295	0.4	727	0.8
Hypertensive	1,184	0.7	381	0.5	803	0.9
Syphilitic	93	0.1	48	0.1	45	0.1
Congenital	115	0.1	43	0.1	72	0.1
Other	280	0.2	107	0.1	173	0.2
Combinations (not included above)	30	<0.1	10	<0.1	20	<0.1
Cardiac disease—type unspecified	273	0.2	91	0.1	182	0.2
Total—cardiovascular diseases diagnosed	3,878	2.2	1,374	1.7	2,504	2.8

*These counts do not represent individuals, but rather diagnoses for individuals. A person may have more than one diagnosis.

incidence in each decade was approximately the same. This cannot be explained either by the sex distribution of the total survey population or by the distribution of those returning for confirmatory films. Further, this sex difference cannot be accounted for geographically since Rutstein and his group[7] found a similar increased incidence of detectable heart disease in females in the Boston survey. In addition, an analysis of those with confirmed cardiovascular disease with regard to cardiac enlargement, cardiac decompensation, and a history of rheumatic fever shows no significant sex difference.

TABLE XIII. AGE AND SEX OF PERSONS WITH DIAGNOSIS OF CARDIOVASCULAR DISEASE FROM PHYSICIANS' REPORTS

AGE GROUP	BOTH SEXES		MALE		FEMALE	
	NO.	RATE PER 1,000	NO.	RATE PER 1,000	NO.	RATE PER 1,000
Under 15*	18	0.7	8	0.7	10	0.7
15–24	169	0.5	69	0.4	100	0.6
25–34	281	0.7	83	0.4	198	0.9
35–44	464	1.3	137	0.8	327	1.7
45–54	811	3.0	254	2.0	557	3.9
55–64	912	5.0	338	4.1	574	5.7
65–74	576	5.9	241	5.5	335	6.2
75 and over	152	5.5	68	5.1	84	5.8
Unknown	5	1.0	1	0.4	4	1.6
Total	3,388	2.0	1,199	1.5	2,189	2.4

*Survey officially included no persons under the age of 15.

A total of 697 cases of previously unknown cardiovascular disease was disclosed by the survey with a distribution according to age, sex, and etiology as shown in Tables XIV and XV. These cases constitute 0.04 per cent of the entire

TABLE XIV. AGE AND SEX OF PERSONS WHOSE CARDIOVASCULAR DISEASE WAS DISCOVERED AS A RESULT OF THE SURVEY

AGE GROUP	BOTH SEXES		MALE		FEMALE	
	NO.	RATE PER 1,000	NO.	RATE PER 1,000	NO.	RATE PER 1,000
Under 15*	9	0.4	2	0.2	7	0.5
15–24	50	0.1	17	0.1	33	0.2
25–34	68	0.2	16	0.1	52	0.2
35–44	90	0.2	30	0.2	60	0.3
45–54	160	0.6	41	0.3	119	0.8
55–64	185	1.0	69	0.8	116	1.2
65–74	101	1.0	39	0.9	62	1.1
75 and over	32	1.2	19	1.4	13	0.9
Unknown	2	0.4	—	0	2	0.8
Total	697	0.4	233	0.3	464	0.5

*Survey officially included no persons under the age of 15.

survey population, 10.6 per cent of those with positive confirmatory 70 mm. films, and 20.6 per cent of the individuals with heart disease confirmed by physicians' reports.

TABLE XV. ETIOLOGY OF CARDIOVASCULAR DISEASE DISCOVERED AS A RESULT OF THE SURVEY

	NO.	RATE PER 1,000
Arteriosclerotic	174	0.1
Rheumatic	114	0.1
Hypertensive	248	0.1
Syphilitic	37	<0.1
Congenital	28	<0.1
Other (including type unspecified)	167	0.1
Combinations (not included above)	5	<0.1
Total	773	0.4

It was possible to obtain a final diagnosis as to the presence or absence of heart disease in 61.3 per cent of those patients who had evidence of cardiovascular abnormality on the confirmatory films (Table XVI). Only 2.6 per cent of those with positive confirmatory films actively resisted medical care. However, 23 per cent were not referred for medical care because they either could not be located because of wrong addresses, did not respond to follow-up letters, etc. 201 additional final diagnostic reports were received too late for tabulation.

TABLE XVI. STATUS OF PERSONS WITH CARDIOVASCULAR DISEASE CONFIRMED ON SECOND 70 MM. FILM

	NO.	(%)
Final diagnosis made	4,091	61.3
Resisted medical care	176	2.6
Died after confirmatory film*	53	0.8
Unable to locate and no response	1,527	23.0
Under study at close of survey†	817	12.3
Total	6,664	100.0

*Includes ten persons for whom a death certificate was obtained which mentioned cardiovascular disease.

†201 additional reports received too late for inclusion in tabulations.

In addition to the 697 patients with previously unknown heart disease, there were 710 patients with previously known cardiovascular disease who were returned to medical care. A total of 1,407 patients with cardiovascular disease was brought under or returned to medical care as a result of this survey (Table XVII). This group represents 0.08 per cent of the entire survey population, 21.2 per cent of those persons who had positive confirmatory 70 mm. films, and 41.3 per cent of the patients with heart disease as confirmed by final diagnoses. The majority (53.6 per cent) of patients with cardiovascular disease confirmed by reports from physicians were under medical care at the time of the survey.

TABLE XVII. CASES OF CARDIOVASCULAR DISEASE DISCOVERED OR BROUGHT UNDER MEDICAL CARE AS A RESULT OF THE SURVEY

	NO.	RATE PER 1,000
Previously unknown cardiovascular disease	697	0.4
Previously known cardiovascular disease—returned to medical care	710	0.4
Previously known cardiovascular disease—not returned to medical care	90	0.1
Under medical care for cardiovascular disease at time of survey	1,818	1.0
Unknown or not stated	73	<0.1
Total	3,388	2.0

In addition to the cost of the general survey, $40,000 was expended in the cardiovascular program. This program disclosed 697 persons with previously unknown heart disease at an additional cost of $58.10 per case. The additional cost of bringing each of the 1,407 individuals under medical care was $29.08 per case (Table XVIII).

TABLE XVIII. COST OF CARDIOVASCULAR PROGRAM

Total expenditures	$40,000.00	
Previously unknown cardiovascular disease*	697 cases	$58.10/case
Brought under or returned to medical care*	1,407 cases	$29.08/case

*This is in addition to the cost of each original 70 mm. survey film which was $0.75.

DISCUSSION AND SUMMARY

While it is clearly recognized that roentgenology of the chest is not the best cardiac case-finding method, the recognition of cardiovascular disease is an integral part of any mass chest x-ray survey. Some plan for the disposition of patients with abnormal cardiovascular silhouettes must be established by any community contemplating such a survey.

In a survey such as this, every effort should be made to avoid suggesting the presence of heart disease where none exists. On the initial screening of the miniature films, 6.3 per 1,000 were suspected of having cardiovascular abnormalities. Reinterpretation by a board of experts, consisting of a radiologist and cardiologist, eliminated 23.2 per cent of these original suspects. Other communities have had the same experience indicating the necessity for re-evaluation of the miniature films by more highly trained physicians if unnecessary expense and anxiety to a fairly large group of individuals are to be avoided.

Many cardiologists question the value of a program which goes beyond informing the patient of a suspected cardiovascular abnormality and advising him to seek medical care. An adequate follow-up program is not only expensive but entails considerable effort and the close cooperation of many individuals, medical groups, and civic organizations. Many patients do not have their own physicians

and must be referred to one from a panel chosen by the local medical society while others must be referred to part-pay or free clinics. A system must be established whereby the physician or clinic reports as to whether or not the patient has been seen. Those patients who do not keep their appointments then have to be contacted, in many cases more than once, either by telephone or letter, in an effort to get them to their physicians. Obtaining final diagnostic reports from physicians involves considerable additional effort. Without adequate clerical and, in particular, social service personnel such a program is impossible.

The results of the cardiovascular program carried on in conjunction with the Los Angeles County Mass Chest X-ray Survey are summarized in Table XIX. There were 1,736,703 satisfactory 70 mm. films taken in the entire survey. Of these 6.3 per 1,000 were suspected of having cardiovascular disease. The group of experts who reviewed the confirmatory 70 mm. films taken of this group found that 23.2 per cent of these individuals had essentially normal cardiovascular silhouettes. A diagnosis of heart disease was confirmed in 76.2 per cent of the patients who were referred for medical care and for whom final diagnostic reports were received.

TABLE XIX. SUMMARY

	NO.	RATE PER 1,000	(%)					
Total satisfactory survey films	1,736,703							
Total abnormal films	67,966	39.1						
Total cardiovascular suspects	10,899	6.3	100					
Returned for confirmatory 70 mm. film	8,532	4.9	78.3	100				
Abnormal, significant for follow-up	6,551	3.8		76.8	100			
Essentially negative	1,981	1.1		23.2				
Patients referred for medical care	5,670	3.3			86.5	100		
Referred to private care	5,148	3.0				90.8		
Referred to other than private care	522	0.3				9.2		
Patients not referred for medical care	881	0.5			13.5			
Final diagnostic report received	4,456	2.6				78.6	100	
No heart disease	1,068	0.6					23.8	
Final diagnosis of heart disease	3,388	2.0					76.2	100
Previously unknown heart disease	697	0.4			10.6			20.6
Previously known heart disease brought under medical care	710	0.4						21.0
Previously known heart disease under medical care at time of survey	1,818	1.0						53.6
Total patients brought under medical care as a result of survey	1,407	0.8			21.2			41.6

The incidence of detectable heart disease in Negroes was twice that expected on the basis of the total survey population, and similarly the incidence of cardiovascular disease detected by the survey in females was almost twice that in males.

There were 697 (0.4 per 1,000 of the survey population) cases of previously unknown heart disease found in the survey and 1,407 (0.8 per 1,000 of the survey population) patients who were brought under or returned to medical care. These groups represent 20.6 and 41.6 per cent, respectively, of those patients in whom

a final diagnosis of heart disease was obtained and 10.6 and 21.2 per cent, respectively, of those whose confirmatory films were considered significant for follow-up.

It should be emphasized that of the cardiac suspects who were referred for further follow-up care, 90.8 per cent received that care through private medical sources. Only 9.2 per cent of the patients were referred to the Los Angeles County Hospital or other public medical services. Contrary to what had been anticipated, the cardiovascular program imposed no additional hardship or burden on the already overtaxed facilities of either the County Hospital or other similar medical agencies.

In the final analysis, the value of a program such as this must be based not only on the number of individuals benefited but also on the cost involved. A cost of $58.10 for each case of previously unknown cardiovascular disease found and $29.08 for each patient brought under or returned to medical care does not seem excessive. This is in addition to $0.75 for each of the original 1,755,001 survey films and does not include any charges for the volunteer services of both medical and nonmedical personnel.

The amount of money and effort that may be expended justifiably, considering the relatively small number of individuals benefited, will depend largely on the funds available and the attitude of the community concerned.

A great number of individuals were responsible for the success of this survey, and we regret that it is impossible to thank each by name. We are particularly grateful to Mr. Acton Barnes of the Los Angeles Tuberculosis and Health Association; Dr. Lester Breslow, Dr. Benno K. Milmore, and Mrs. Penny Rasmussen of The Bureau of Chronic Diseases, Department of Health, State of California; and the United States Public Health Service.

REFERENCES

1. Cauley, J. H.: The Results of the Boston Chest X-ray Survey, New England J. Med. **243**:631, 1950.
2. Christie, A. C.: Some Medical and Roentgenological Aspects of Mass Chest Surveys, Am. J. Roentgenol. **61**:147, 1949.
3. Flancher, L. H.: Case Finding in Iowa, Am. Rev. Tuberc. **57**:375, 1948.
4. Green, M. H.: Cardiovascular Abnormalities Noted in a Mass Survey for Tuberculosis, Am. Rev. Tuberc. (Suppl.) **41**:148, 1940.
5. Mathisen, A. K., Morris, W., and Wilson, G. B.: The Value of Miniature Radiography in the Detection of Heart Disease, Am. Heart J. **39**:505, 1950.
6. Robins, A. B., and Ehrlich, D. E.: Group X-ray Surveys in Apparently Healthy Individuals, Radiology **34**:595, 1949.
7. Rutstein, D. D., Williamson, C. R., and Moore, F. E.: Heart Disease Case Finding by Means of 70 Millimeter Photofluorographic Films, Group I, Circulation **4**:641, 1951.
8. Williamson, C. R., Moore, F. E., and Rutstein, D. D.: Heart Disease Case Finding by Means of 70 Millimeter Photofluorographic Films, Group II, Circulation **4**:652, 658, 1951.
9. Schwartz, B., and Berman, B.: Incidence of Heart Disease in Mass X-ray Surveys, J.A.M.A **149**:734, 1952.
10. Selzer, A., Harrison, M. B., and Daniloff, G. T.: The Detection of Unsuspected Heart Disease in Photofluorographic Chest Surveys, Am. Heart J. **42**:355, 1951.

SOME EPIDEMIOLOGIC ASPECTS OF BLOOD PRESSURE AND ITS RELATIONSHIP TO DIET AND CONSTITUTION WITH PARTICULAR CONSIDERATION OF THE CHINESE

A Review of the Pertinent Literature of the Past 40 Years

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Flushing, N. Y.

LITERATURE on high blood pressure in its various aspects presents a wealth of information today. If one is looking, however, for reliable data on physiologic blood pressure as it occurs in different groups of people in various parts of the world, there is a dearth. Whatever data exist are scattered throughout the medical and anthropological literature. Much of this information is sketchy and cannot be used for statistical evaluation.

An attempt will be made here to present a summary of the available literature on blood pressure levels in various groups of Chinese people with particular attention to epidemiologic data and methodology. Thereafter, a statistical evaluation of some of the differences in mean blood pressure levels found in the literature reviewed will be made. In searching for an explanation of these differences, various intrinsic and extrinsic factors will be discussed in their relationship to blood pressure levels; among the former are age, height, weight and body build. Diet will be the only extrinsic factor discussed.

There are a number of papers, most of them published between 1920 and 1937, dealing with measurements of blood pressure in various groups of the Chinese people in different parts of China. The total number of people examined, as gathered from the papers reviewed,[1-10] up to 1937 had been about 23,000, an extremely small number among a population of at least 400 million (roughly 0.005 per cent). Outside of China only one small group of 239 Chinese people living in Montreal, Quebec, had been examined in 1934[11] and a few students in Minnesota in 1933.[12] A breakdown of a total of 19,064 people, for whom age and sex distribution data are available, is found in Table I.

More than 99 per cent of the people examined were below the age of 55, 75 per cent between the ages of 14 and 40. The sex distribution is very unequal: 20,499 males to 1,539 females; this number includes in addition to the above total 2,159 males and 815 females on Formosa. This is a ratio of 92 per cent males to 8 per cent females. The occupational distribution of 17,853 people in China, the total for whom such data are available, is shown in Table II.

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TABLE I

AGE GROUP	TOTAL NUMBER	MALE	FEMALE
Below 14	198	191	7
14–19	1,635	1,589	46
20–24	2,594	2,434	160
25–29	4,785	5,584	201
30–34	4,207	4,103	104
35–39	2,912	2,838	74
40–44	1,548	1,478	70
45–49	829	790	39
50–54	290	273	17
55–59	62	58	6
60–64	2	2	0
65–69	2	2	0
Total	19,064	18,340	724

TABLE II

OCCUPATIONS	APPROX. TOTAL
Students	1,559
Merchants	8,000
Professionals	7,000
Coolies	798
Clerks	126
Technicians	62
Hunters, peasants, etc.	398
Total	17,853
Unclassified	1,336

From this it follows that more than 90 per cent of these 17,853 people in China belonged to the upper socioeconomic class, being merchants and professionals, who were able to buy life insurance between 1924 and 1935. Only a very small percentage of the Chinese people was able to buy life insurance during that period. Approximately 9 per cent of these 17,853 people have been students on both the undergraduate and graduate level. Less than 5 per cent have been classified as coolies representing the lowest economic strata. Among the 239 Chinese examined in Montreal, Quebec, in 1934, 42 per cent were laundry workers, 15 per cent cooks, 13 per cent merchants, and less than 10 per cent restaurant owners.

In regard to the technic used by the various investigators (Table III) in taking and recording their blood pressure measurements, the available data are very scanty. All authors apparently used the auscultatory method. Out of five authors reporting which arm they used in their subjects, four used the right, and one the left arm. Position of the subject, whether reclining or sitting, is mentioned by almost all investigators, namely ten, four took the measurements with their subjects in the reclining position and six in the sitting position. Only

TABLE III. SUMMARY OF DATA ON METHODS AND CIRCUMSTANCES IN STUDIES OF BLOOD PRESSURE AMONG VARIOUS GROUPS OF CHINESE AND AMERICANS BETWEEN 1910 AND 1937

LOCATION AUTHOR, YEAR	TOTAL NO. EXAMINED		OCCUPATION	METHOD	INSTRUMENT	ARM		POSITION		CONDITION		TIME OF DAY		TIME OF YEAR			
	MALES	FEMALES				RIGHT	LEFT	RE-CLIN.	SIT.	CAS-UAL	REST-ING	A.M.	P.M.	WTR.	SPR.	SUM.	FALL
Canton, China Cadbury, 1922	774	0	Students	auscult.	Nicholson sphygmomanometer	?	?	?	?	?	?	?	?	?	?	?	?
Szechwan, China Kilborn, 1924	759	0	Students	auscult.	Nicholson sphygmomanometer	X	0	0	X	X	0	0	X	0	25%	0	75%
Changsha, Hunan Kao, 1921 China	246	0	Students	auscult.	Tycos sphygmomanometer	?	?	X	0	0	X	0	X	0	X	X	0
Peiping, Tienstin, Shanghai, Chungking, Hongkong, Manila, Singapore, Batavia Ling, 1924-35	15,114	493	Life insurance risks, mainly merchants and professionals	auscult.	Baumanometer	?	?	0	X	X	0	?	?	?	?	?	?
Peiping, China Tung, 1928-29	1,233	0	Manual and white collar workers	auscult.	Hg-manometer		X	0	X	0	X	?	?	?	?	?	?
Peiping, China Cruikshank, 1923	75	0	Students, technicians, coolies	auscult.	?	?	?	X	X	X	X	?	?	0	0	X	0

Shaoing, Chekiang Ling, 1926	182	37	Various	auscult.	Nicholson sphygmomanometer	?	?	X	0	0	X	?	?	?	?	?	?
Szechwan, China Aboriginates Morse & Beh, 1937	398	0	Hunters, shepherds, peasants	auscult.	Nicholson and Tycos sphygmomanometer	X	0	0	X	X	0	X	X	?	?	?	?
Formosa Rai, 1935	2,159	815	Life insurance risks	auscult.	?	X	0	?	?	X	0	?	?	X	0	X	0
Montreal, Can. Krakower, 1933	236,121	3 (?)	42% laundry workers	auscult.	Hg-manometer	?	?	0	X	X	0	0	X	?	?	?	?
Minneapolis, U. S. A. Diehl, 1933	702	0	Students	auscult.	?	?	?	?	?	?	?	?	?	?	?	?	?
Eastern U. S. A. Symonds, 1907-19	150,419	11,937	Life insurance risks	palpatory & auscult.	?	?	?	?	?	?	?	?	?	?	?	?	?
San Francisco, U. S. A. Alvarez, 1918-21	15,000	0	Students, freshman	palpatory	Aneroid and 3 Hg-sphygmomanometer	?	?	X	0	?	?	?	?	?	?	?	?
New York, U. S. A. Woley, 1910	1,000	?	Life insurance risks	palpatory	2 types (?)	?	?	0	X	?	?	?	?	?	?	?	?

one author mentions that he took his measurements after his subjects had rested for at least 20 minutes. Uniformity seems to exist in recording the blood pressure. Every author reports that he had read the systolic pressure at the so-called first phase of the cardiac cycle, i.e., when the first clear sound reappears after having inflated the cuff well above the level of disappearance of all sounds. The diastolic pressure has been read at the so-called fourth phase, i.e., when the clear sound changes its character to muffled after deflating the cuff. Eight authors mention the time of the day when their measurements were taken: three took their readings in the forenoon, five in the afternoon. Only one investigator after one year did a follow-up in 100 of his subjects[5]: 30 per cent showed no change, 49 per cent a decrease of 5 mm. Hg or more, and 21 per cent an increase of 5 mm. Hg or more at the second examination. About 50 per cent of the changes affected both phases, systolic and diastolic; more than 30 per cent affected the systolic pressure only.

As to the time of the year used for their observations: three times as many observations have been made between April and October as during the winter months. Only three authors mention that they observed no seasonal variation in their blood pressure levels; none of the remaining authors mentions this question.

In comparing the mean blood pressures of the various Chinese groups with the blood pressure levels of corresponding groups in the U. S. A. the standards used for comparison by the different authors are derived mainly from three sources.[13-15] In the papers by Symonds, Alvarez, and Woley[13-15] one finds that measurements have been reported for a total of 166,419 people in these three papers, almost eight times as many as in China. (This is still only 0.1 per cent of the total population of the U. S. A.) The age range is 15 to 65 (with approximately one-third between 25 and 34, and about 1 per cent 60 years and over). Although no exact figures are given on sex distribution, it is apparent that more than 90 per cent of the total examined were males. In regard to their occupational distribution all that can be said is that 151,419, or over 90 per cent, constituted healthy life insurance applicants whereas the remaining 9 per cent were students (freshmen at the University of California).

The technique used by the three authors differs considerably: the readings on the 151,419 life insurance risks have been taken with the subject sitting, while the students have been examined in the reclining position. Woley and Alvarez used the palpatory and auscultatory method, however, the latter only in 66,000 subjects examined between 1916 and 1919. The readings have been recorded at the first phase for the systolic and the fourth phase for the diastolic pressure. No follow-up has been recorded in any of these groups. No mention has been made of the season or time of day when measurements had been taken.

From the foregoing it becomes apparent that the data taken from the American authors do not represent good standards for comparison with the Chinese data. First, the techniques used are quite different. The majority of the American data up to 1922 are based on the palpatory method, whereas all the Chinese data are based on the auscultatory method. "Comparative tests by the two methods indicate that systolic pressures determined by the ausculta-

tory method are usually 5-15 mm. higher than they are by the palpatory method"[62] (p. 65). Secondly, the various groups examined in the U. S. A. and in China are not strictly comparable because of their different socioeconomic level. Thus it appears, if one would like to make a comparison between two groups in spite of the aforementioned shortcomings that the students should represent the best comparable groups, the life insurance applicants the second best.

In Table IV are summarized the results of a statistical evaluation of the differences found in mean systolic blood pressure values between specific age groups of some Chinese and American students. Among the University of California freshmen, Alvarez took his measurements by the palpatory method with his subjects in the reclining position, whereas Kilborn with the West China University students used the auscultatory method with his subjects in the sitting position. If these differences in technique did not exist the difference in blood pressure levels between the two groups would be even greater for the following reasons: readings taken in the reclining position and by the palpatory method tend to be lower than readings taken in the sitting position and by the auscultatory method.

No significant tests could be made in comparing the pressure levels of the largest groups examined, the life insurance risks, because no distribution data of blood pressure levels had been given by the authors.

The next question presenting itself is: What causes considerable differences in blood pressure levels between Chinese and Westerners? Two factors stand out among several others mentioned by every investigator in China. One is diet, as an important factor in the environment which will be dealt with later on, and the other is the mental attitude or philosophy reflecting a state of society where there is much less stress producing competition and aggressiveness. Another important factor affecting blood pressure levels is the age-weight-height relationship, largely determined by the hereditary constitution of the individual. It appears from the literature covering various geographical areas[1-3,5,9,11,14,16-18] that the systolic as well as the diastolic blood pressure levels increase with age from early infancy to young adulthood where they may remain stationary or even decrease slightly during the third decade. After the third decade the levels of both pressures start rising again up to the end of the seventh decade.[20-26] After that, data which had become scant because of the lack of subjects studied seem to indicate another leveling off. This correlation between age and blood pressure levels, however, seems to occur only in urbanized population groups in Asia, Europe, and America, while it does not seem to exist among the primitive groups examined in Asia, Africa, and America.[8,9,19,27] However, only a very small number of some of these primitive groups have been studied who were all living as hunters, shepherds, or fishermen on a nomadic or seminomadic level. The number of older people examined, past the age of 45, is probably too small to have statistical meaning. The people in the older age groups of those primitives showed a definite fall in blood pressure levels as compared to the age groups of 20 to 40. Robinson and Brucer,[23] however, have shown in their series of 7,478 males in the Chicago area that, if they eliminated all persons with pressures

TABLE IV. COMPARISON OF MEAN SYSTOLIC BLOOD PRESSURE LEVELS IN SEVERAL GROUPS OF CHINESE AND AMERICAN STUDENTS

	AGE	NO. EXAMINED IN EACH GROUP	MEAN SYSTOLIC BLOOD PRESSURE MM. HG	STANDARD DEVIATION	AGE	NO. EXAMINED IN EACH GROUP	MEAN SYSTOLIC BLOOD PRESSURE MM. HG	STANDARD DEVIATION	DIFFERENCE BETWEEN MEANS
		West China Union University Szechwan, 1924				University of California freshmen 1918-21			
	16	46	108	10	16	94	129.3	12.5	21.3**
	17	68	112	11.2	17	541	130.1	12.2	18.1**
	18	102	109	11.8	18	1216	130.0	13.4	21.0**
	19	106	110	11.2	19	1066	128.2	13.6	18.2**
	20	93	114	11.0	20	742	129.5	13.8	15.5**
	21	61	115	11.0	21	623	127.6	12.8	12.6**
	22	50	115	13.0	22	422	128.3	13.8	13.3**
	23	53	109	10.9	23	335	129.1	13.9	20.1**
	24	35	112	10.0	24	231	129.0	12.6	17.6**
Total no. examined		614				5270			

		Canton Christian University, 1922				High School, San Francisco, Cal.[15] University of California freshmen 1918-21			
	AGE 15	90	97	12.0	15	140	118.6	12.5	21.6**
	16	101	100	12.1	16	94	129.3	12.5	29.3**
	20	46	103	12.5	20	742	129.5	13.8	26.5**
Total no. examined		237				976			
		First, Middle and Normal School, Changsha, Hunan, 1921				University of California freshman 1918-21			
	AGE 18	45	115	8.8	18	1216	130.0	13.4	15.0**
	19	47	103	15.4	19	1066	128.2	13.6	25.2**
	20	58	120	10.1	20	742	129.5	13.8	9.5**
Total no. examined		150				3024			

**This difference between the mean blood pressure levels in the two groups compared is statistically significant according to the normal curve test at 0.01 level.

over 140 systolic and 90 diastolic, the mean blood pressure of the remaining 6,485 males does not rise with age. This is similar to the findings in the primitive groups, although the levels may still be higher in the various age groups. This holds only for males; females do show a definite rise of their pressure levels with age, even in the "normalized" groups. All the studies mentioned are cross sectional and not longitudinal as might be desirable for further clarification of the age relationship with blood pressure.

In regard to height and its relationship to blood pressure levels, the evidence from the literature shows a positive correlation during the period of growth and development of the individual.[1,16,17,28] In the adult, however, this correlation becomes less well established as some excellent studies indicate.[10,18,22,25,26,29,30,31]

Weight, on the other hand, seems to carry its positive relationship with blood pressure levels from infancy throughout adulthood as attested by many investigations.[1,2,10,16-18,22,24,25,27-30] However, more recent studies have shown that the correlation between weight and blood pressure levels is actually a correlation between body build and blood pressure levels. Only certain body types, the so-called lateral or broad build (endo-mesomorphic according to Sheldon) type will put on considerable amounts of weight during any time of their life, whereas the linear, slender ectomorph will show very small variations in his weight throughout his life. In this connection mention should be made of errors in measuring the blood pressures of obese people due to the use of standard cuffs which are usually too small for obese people. Readings tend, therefore, to be higher in obese people than they really are.[60]

If one tries to apply these findings to our problem one might ask the question whether the differences in blood pressure levels found between Chinese and American students could be explained simply by differences in body build? There is evidence showing the mean height and weight in corresponding age groups to be definitely lower in the Chinese than in the Americans.[4,37,38] In regard to body build only one study on 150 students, nurses, and doctors at Peiping Union Medical College is available, showing the great majority (137 of 150) belong to the linear body type in both sexes, only one belonged to the lateral build and twelve were intermediate. One study on a group of 100 mental patients in institutions in Peiping by Stevenson showed 99 per cent of these patients to belong to the so-called leptosome type according to Kretschmer. This leptosome would correspond to the linear- or ectomorph-build type mentioned previously. In view of the highly selected sample this study has certainly no application to the general population in China or even in Peiping, if consideration is given to the regional differences existing between North and South China.

In this connection one other constitutional factor deserves mention which may have some bearing on blood pressure levels in males. This is the greater amount of "femaleness" as found in the Chinese male by several authors.[40-42] Femaleness in this connection refers mainly to the amount and distribution of body hair. The differential in blood pressure levels between males and females under 45 appears fairly well established.[23,33,34,43,44] Females seem to have significantly lower pressures than males up to age 45. In children, however, this may not be the case. This appears to be true also in China as far as one can tell

from the paucity of data on females. Whether the greater "femaleness" of the Chinese male may account in part for his lower blood pressure levels remains an interesting speculation at this time. If this was so, it would not explain why the same differential seems to exist between the pressure levels of the Chinese male and female which exist in the Caucasian. One would expect rather a narrowing or even disappearance of this differential, if "femaleness" was a factor.

From the foregoing it becomes apparent that the evidence available does not suffice to explain the differences in blood pressure levels between Chinese and American groups simply on the basis of differences in height and weight or body build.

Diet as one of the most important factors in the environment may affect blood pressure levels in two ways: first indirectly through its influence on the weight aspect of the body build and secondly directly through the effect of one or several nutrients on the blood pressure. The foregoing remarks about the relationship between body build and blood pressure explain easily the first indirect effect of diet on blood pressure levels and need no further elaboration.

In regard to the second or direct effect of diet there are only very few investigations available where the authors have tried to make diet as a whole the main variable. There are two papers by German authors,[21,45] showing that a vegetarian diet coincided with significantly lower blood pressure levels than a mixed diet (meat, fish, fowl) in comparable groups of people (monks). The other paper deals with blood pressure levels in 60 meatless and 6 meat-egg-dairy-less vegetarians as well as 40 alcoholics who also smoked. All levels except those of the last group were well below various European and American standards of that period (1930). Guenewardene's[20] findings in four different groups of males between the ages of 30 and 70 in Ceylon seem to confirm the results of the German authors inasmuch as the group of rickshaw men on a rice-vegetable diet had the lowest pressure, the meat-eating Moslems had the highest pressures. There are, however, other factors such as differences in the amount of exercise and the amount of food eaten which may play an important part in determining the blood pressure levels of these groups.

That blood pressure levels can be low also on an almost 100 per cent meat diet has been shown by Thomas[46] in his examination of 142 Eskimos in Greenland aged 40 to 60, with a mean blood pressure of 129/76. Ganssiein (as quoted by Bock [47]) observed marked changes in the peripheral capillaries of the vascular system in normal subjects changing from a complete meat diet to a complete vegetarian diet. It would be interesting to find out whether those same changes occur in Eskimos, for instance.

A paper by Donaldson[48] shows a possible sound approach to an experimental investigation in human beings of this important relationship. However, the experimental data presented are based on the findings in only five students observed over 5 weeks. Whether the changes in blood pressure levels observed by this author when his subjects changed from a vegetarian diet to a mixed diet (meat) are significant appears questionable. There are observations by other authors, Newburgh,[49] McClellan and DuBois as quoted by Bishoff[50] on one and two experimental subjects, respectively, on extremely high-meat diets who showed

no significant changes in the blood pressure levels of these subjects in spite of definite kidney damage in Newburgh's subject who ate 337 grams of protein derived from beef and veal daily with a large proportion derived from liver. Other authors (Squier and Newburgh,[51] Mosenthal, as quoted by Bishoff,[50] Strouse and Kelman[52]) have confirmed these findings in a few normal and larger groups of patients. In experimental animals (rabbits) Nuzum[53] and co-workers have been able to produce increased blood pressure levels with extensive arteriosclerosis by feeding them various excessive protein diets for 2 years. A liver diet produced the highest blood pressure levels and the most advanced changes showing that the kind of protein seems to be of importance in producing the reported changes.

The only other nutrient studied extensively in relation to blood pressure is sodium chloride; however, most of the investigations in human subjects have been carried out in hypertensive persons with a minority of hypertensives showing a definite fall in their blood pressure levels after sodium restriction.[54] In the rat the experimental evidence on the correlation between sodium level of the diet and blood pressure levels is much more evident than in any other animal including man. Rats respond also to other dietary imbalances with rises in blood pressure levels, e.g., diets low in riboflavin[57] or high in tyrosine.[58] Finally, the important experimental work by Best and Hartrof[59] should be mentioned showing that a deficiency of choline in the diet of recently weaned rats lasting only a few days may lead to severe hypertension with cardiovascular renal disease later in life.

Before any conclusions are drawn from the literature reviewed it should be pointed out again that the information contained in many of these papers is sketchy and incomplete in regard to such details as methods of measurement, time of measurement, person who took measurements, etc. The lack of this detailed information does indeed make the comparability of the results of the various investigators questionable. With this limitation in mind it may be said in conclusion that it is evident that blood pressure levels in the individual are determined to a certain extent by two general factors: one is constitutional possibly determined by heredity and expressed in the body-build type with its potential of growth in three dimensions, the other environmental influenced by nutrition from, or possibly even before, birth. The influence of this second factor has been much less explored than the first one and offers a wide open field for investigation.

REFERENCES

1. Cadbury, W. W.: Blood Pressure of Normal Cantonese Students, Arch. Int. Med. **30**:362, 1922; also China M. J. **37**:715, 1923.
2. Kilborn, Leslie G.: Blood Pressure of Szechwanese Students, China M. J. **40**:1, 1926.
3. Kao, C. L.: Blood Pressure of Hunan Students, Nat. Med. J. China **8**:10, 1922.
4. Ling, W. K.: The Blood Pressure of the Chinese; Statistical Study of 20,948 Life Insurance Applicants, Chinese M. J. **50**:1773, 1936.
5. Tung, Chen-Lang: Blood Pressure of Northern Chinese Males, Chinese J. Physiol. **4**:117, 1930; also same, J. Rep. Ser. 1, 1928.
6. Cruikshank, E. W. H.: Physiological Standards in North China: Blood Pressure Studies; Alveolar Air Gases, China M. J. (suppl.) **37**:1, 1923.
7. Ying, Y. Y.: Blood Pressure of Healthy Individuals in Shaohing, China M. J. **40**:641, 1926.
8. Morse, W. R., and Beh, Y. T.: Blood Pressure Amongst Aboriginal Ethnic Groups of Szechwan Province, West China, Lancet **1**:966, 1937.

9. Kilborn, Leslie G.: A Note on the Blood Pressure of Primitive Races, With Special Reference to the Miao of Kweichow, Chinese J. Physiol. (no. 1) **11**:135, 1937.
10. Kiroku, Rai: Statistische Betrachtungen ueber den Blutdruck von geseunden lebensversicherten Formosa Chinesen, Taiwan Igakkai Zasshi **35**:956 1936.
11. Krakower, A.: The Blood Pressure of Chinese Living in Eastern Canada, AM. HEART J. **9**:396, 1934.
12. Diehl, Harold S.: Racial Differences in Blood Pressure, Minnesota Med. **14**:726, 1933.
13. Symonds, B.: The Blood Pressure of Healthy Men and Women, J.A.M.A. **80**:232, 1923.
14. Alvarez, Walter C.: Blood Pressure in 15,000 University Freshmen, Arch. Int. Med. **32**:17, 1923.
15. Woley, H. P.: The Normal Variation of the Systolic Blood Pressure, J.A.M.A. **55**:121, 1910.
16. Faber, Harold K., and James, C. A.: The Range and Distribution of Blood Pressure in Normal Children, Am. J. Dis. Child. **22**:7, 1921.
17. Burlage, Stanley R.: Blood Pressure and Heart Rate in Girls During Adolescence, Proc. Soc. Exper. Biol. & Med. **19**:247, 1922.
18. Chamberlain, W.: Observations on the Influence of the Philippine Climate on White Males in the Philippines, J. Sc. **6**:437, 1911.
19. Donnison, C. P.: Blood Pressure in the African Native, Lancet **1**:7, 1929.
20. Gunewardene, Hugo O.: High Blood Pressure and Its Common Sequelae, London, 1935, Baillière, Tindall & Cox, p. 23.
21. Raab, W., and Friedman, R.: Das Verhalten der Kreislauforgane bei Vegetariern, Ztschr. f. klin. Med. **130**:505, 1936.
22. Schuerman, Albert G.: Blood Pressure in Relation to Age, Weight and Height, Virginia M. Monthly **68**:660 1941.
23. Robinson, S. C., and Brucer, M.: Range of Normal Blood Pressure, Arch. Int. Med. **64**:409, 1939.
24. Vaughan, Warren T., and Graham, W. R.: Hypotension in the South, South. M. J. **23**:12, 1930.
25. Huber, E. G.: Systolic and Diastolic Blood Pressure in Healthy Males, Human Biol. **5**:4, 1933.
26. Reed, Lowell J., and Love, A. G.: Biometric Studies on U. S. Army Officers—Somatological Norms, Correlations, and Changes With Age, Human Biol. **4**:509, 1932.
27. Kean, B. H.: Blood Pressure of Cuna Indians, Am. J. Trop. Med. **24**:341, 1944.
28. Michael, May: A Study of Blood Pressure in Normal Children, Am. J. Dis. Child. **1**:272 1911.
29. Faber, Arne: Readings of Blood Pressure of 1,000 Healthy Individuals Aged 20-25, Scandinav. Arch. f. Physiol. **45**: 1924.
30. Wunderlich, H.: Blood Pressure and Pulse in Well Developed German Students and Their Relation to Various Bodily Norms, Ztschr. f. Konstitutionslehre **38**:349, 1934.
31. Borcas, Pondorinath: Contribuição ao Estudo de Tensões arteriãos em Individuos normais de Goa, Arqu. d. Escol. Med. Chir, Nova Goa **10**: 1935.
32. Robinson, S. C.: Hypertension in Relation to Height; Its Variation With Body Build and Obesity, J. Lab. & Clin. Med. **26**:930, 1941.
33. Robinson, S. C., and Brucer, M.: Body Build and Hypertension, Arch. Int. Med. **66**:393, 1940.
34. Robinson, S. C., and Brucer, M.: Hypertension, Body Build and Obesity, Am. J. Med. Sc. **199**:819, 1940.
35. Larimore, Joseph W.: A Study of Blood Pressure in Relation to Types of Body Build, Arch. Int. Med. **31**:567, 1923.
36. Schaposnik, F.: Tensión Arterial y Biotipo, Rev. Clin. Espan. **24**:26, 1947.
37. Wu, Chentze Haiang, and Soong, Shao-Chung: Growth Rate of Chinese, Am. J. Phys. Anthropol. **28**:357, 1941.
38. Uttley, K. H.: Heights and Weights of Cantonese Adults, Tr. Roy. Soc. Trop. Med. & Hygiene **35**:4, 1942.
39. Willner, Otto: Mitral Stenosis and Measurements of Normals Among Chinese, Am. J. Med. Sc. **180**:200, 1930.
40. Stevenson, P. H.: Chinese Constitutional Differential and Kretschmerian Typology, Human Biol. **9**:451, 1937.
41. Frazier, Chester H., and Chiung, Li Hung: Racial Variations in Immunity to Syphilis, 1948, University of Chicago Press.
42. Lasker, Gabriel W.: Migration and Physical Differentiation, Am. J. Phys. Anthropol. N. S. **4**:273, 1946.
43. Pereira, Manuel: A Pressão Arterial no Biotipo Feminino, Argu. Circurgia Clin. e Experiment **6**:1302, 1942.
44. Boynton, R. E., and Todd, R.: Blood Pressure Readings of 75,258 University Students, Arch. Int. Med. **80**:454, 1947.
45. Saile, Felix: Ueber den Einfluss der vegetarischen Ernaehrung auf den Blutdruck, Med. Klin. **25**:929, 1930.

46. Thomas, W. A.: Health of a Carnivorous Race; Study of Eskimo, J. A. M. A. **88**:1559, 1927.
47. Bock, Karl A.: Vergleichende Untersuchungen ueber die Krankheitsgruppe der Vasoneurotischen Diathese, Ztschr. f. d. ges. exper. Med. **72**:595 1930.
48. Donaldson, Arthur: The Relation of Protein Food to Hypertension, California & West. Med. **24**:3, 1926.
49. Newburgh, L. H., and Clarkson, S.: Experimental High Protein Diet in Man, Arch. Int. Med. **37**:733, 1926.
50. Bischoff, Fritz: The Influence of Diet on Renal and Blood Vessel Changes, J. Nutrition **5**:431, 1932.
51. Squier, T. L., and Newburgh, L. H.: Renal Irritation in Man From High Protein Diet, Arch Int. Med. **28**:1, 1921.
52. Strouse, Sol., and Kelman, Sara: Protein Feeding and High Blood Pressure, Arch. Int. Med. **31**:151, 1923.
53. Nuzum, Franklin, et al.: Arteriosclerosis and Increased Blood Pressure, Arch. Int. Med. **37**:733, 1926.
54. Page, Irving, and Corcoran, A.: Dietary Treatment of Hypertension, J. Clin. Nutrition **1**: 1952.
55. Selye, Hans, Hall, C. E., and Rowley, E. M.: Malignant Hypertension Produced by Treatment With Desoxycorticosterone and NaCl, Canad. M. A. J. **49**:88, 1943.
56. Sapirstein, L. A., Brandt, W. L., and Drury, D. R.: Production of Arterial Hypertension in the Rat by Substitution of Hypertonic NaCl Solution for Drinking Water, Am. J. Med. **8**:525, 1950.
57. Calder, R. M.: Nutritional Deficiencies as Cause of Elevated Blood Pressure in Rats, J. Exper. Med. **76**:1, 1942.
58. Martin, G. J.: Hypertensive Effects of Diets High in Tyrosine, Arch. Biochem. **1**:397, 1943.
59. Best, C. H., and Hartrof, W. S.: Nutrition, Renal Lesions and Hypertension, Federation Proc. **8**:610, 1949.
60. Ragan, C., and Bordley, J., III: The Accuracy of Clinical Measurements of Arterial Blood Pressure With a Note on the Auscultatory Gap, Arch. Int. Med. **69**:504, 1941.
61. Kean, B. H., and Hammill, John F.: Anthropathology of Arterial Tension, Arch. Int. Med. **83**:355, 1949.
62. Wiggers, C. J.: Physiology in Health and Disease, Philadelphia, 1944, Lea & Febiger.

DISSECTION OF THE VECTORCARDIOGRAM: DIFFERENTIAL VECTORCARDIOGRAPHY

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A VECTORCARDIOGRAM is a record of the electrical activity of the heart during a complete cycle and consists of four basic components: P and QRS loops representing atrial and ventricular activation, and Ta and ST-T loops representing atrial and ventricular recovery (repolarization), respectively. Vectorcardiograms may be obtained by reconstruction from orthogonal leads or by synthesis by a cathode-ray oscilloscope. The former method is tedious and impractical and requires multichannel recorders. The vectorcardiograms obtained with the cathode-ray oscilloscope have in general not been satisfactory because of photographic difficulties in distinguishing the individual characteristics of the component four loops. Because the heart beat is a repetitive cycle, the cathode-ray beam returns to the isoelectric point (origin of the vector loop) for a large part of the heart cycle, producing fogging in this area. The intimate details of the origin and termination of the various loops[1] are obscured especially by the slow inscription of the ST-T loop and the long duration of the T-P interval during which the beam is near the origin of the loop.

Four approaches have been employed to overcome these difficulties: (1) cinematography, (2) electrovectorcardiographic method of Milovanovich, (3) selective unblanking, and (4) selective dimming of the beam intensity. The method of cinematography is expensive, not practical, and the separation of the component loops is haphazard. In addition, it is rather inconvenient to measure the various areas and the angles between the loops from film strips. In the second method[2] the photographs are made during the horizontal movement of the film, while a loop is inscribed. By this maneuver, the QRS loop is uncoiled, revealing the direction of the loop. However, there is considerable distortion of the QRS loop. This method is not applicable to the definitive study of the P and ST-T loops. The third method, differential vectorcardiography, was introduced by Briller and associates in 1950.[3] Their special apparatus was designed to separate

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and record the P, QRS and T loops without distortion. Their apparatus consisted of a three-channel amplifier, a synchronized timing unit, a special dual-beam cathode-ray oscilloscope, a modified electronically operated camera, and a three-channel direct-writing recorder. Briller and his associates have not yet reported their subsequent experience with this apparatus. A fourth method, dimming of the intensity of the beam during slow movement or intensification during fast movement (inscription of the QRS), permits a brighter picture of the QRS loop but does not isolate the component loops.[4]

In view of the importance of obtaining separated components of the vectorcardiogram, the present authors have developed "an electrical dissector" (selective blanker or unblanker) which can be used with commercially available apparatus, cathode-ray oscilloscopes, preamplifiers, ordinary camera, and a single-channel direct-writer. The other advantages and disadvantages will be discussed below. The results of our study of the P loops in right and left atrial hypertrophy and of the ST-T loop in hypertrophy and acute infarction will be reported elsewhere.

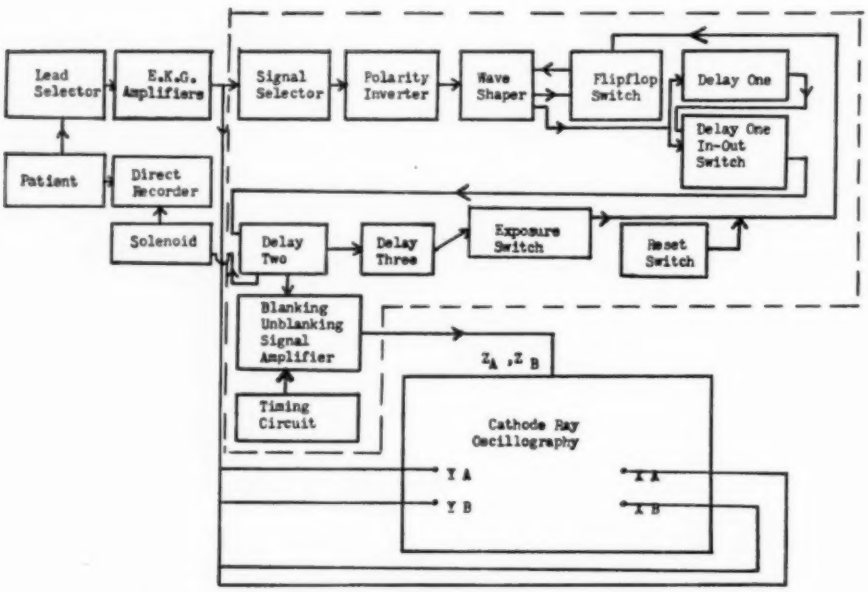

Fig. 1.—Block diagram of selective dissector vectorcardiograph.

APPARATUS

The block diagram of the apparatus is shown in Fig. 1. The dissector is enclosed by interrupted lines.

Patient voltages are obtained from properly placed German silver electrodes. The lead selector of the present device allows for the use of either the tetrahedral or cube reference system. For the purpose of selective blanking or unblanking, any reference system may be utilized. The output of the lead selector is fed into three electrocardiograph amplifiers. The three voltages obtained from the input switch represent the X, Y, and Z projections of the heart voltages. XY represents the frontal plane, YZ the sagittal, and XZ the horizontal plane. The gain of each amplifier is individually controlled and is calibrated by the application of a standard millivolt.

The outputs of the three amplifiers are then applied both to the various inputs of a standard dual-beam oscillograph (in this case Dumont 279), and to the signal selector of the "dissector." The signals to the oscillograph are represented on the screen of the cathode-ray tube. The signal selector allows a choice of any one of the outputs of the electrocardiographic amplifiers which has the most appropriate QRS signal for actuating the dissector. In actual practice, the initial portion of the QRS signal can be used, whether positive or negative. The apparatus contains a polarity inverter which may be used when necessary to change the polarity of the QRS signal. The signal is then applied to a wave shaper, which by the use of appropriate filters responds to sharp pulses, such as QRS waves, and is relatively insensitive to waves such as the usual P and T waves, and somatic tremors. The QRS wave is used because it has a higher voltage, is more easily recognizable, and is more reliable in appearance. The wave shaper modifies the signal to the form of a pulse suitable in amplitude and shape for triggering the subsequent circuits. This pulse is then applied to the flipflop switch, which renders the wave shaper inoperative to subsequent signals

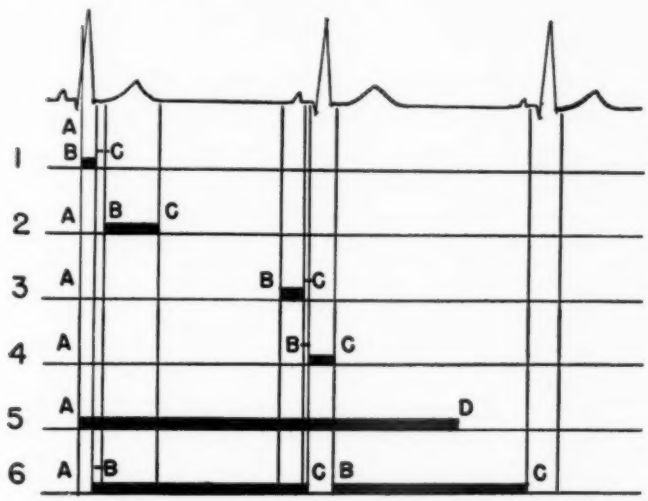

Fig. 2.—Diagram of time sequence operation of selective blanker-unblanker device. *A*, Triggering signal is received. *A-B*, Delay 1, delay period before unblanking. *B-C*, Delay 2, duration of unblanking. *A-D* (row *5*), Period during which apparatus cannot be triggered by any other signal. *A-D* is controlled by the sum of Delays 1, 2, and 3. In row *1*, there is selective unblanking of the terminal portion of the QRS loop, the initial part of which supplies the triggering signal. Delay 1 is out of the circuit. In row *2*, selective unblanking of the ST-T complex is obtained. In row *3*, selective unblanking of the P wave is obtained. In row *4*, selective unblanking of the first QRS complex following the triggering QRS signal is obtained. In row *6*, an alternate method of obtaining an isolated QRS loop. The beam is blanked from *B-C*, and becomes intense during the period *C-B*.

from the signal selector until the flipflop switch is reset. This pulse is now also applied to Delay 1 and to Delay 1 in-and-out switch. If Delay 1 is out of the circuit, this pulse is presented to Delay 2 without delay. If Delay 1 is in the circuit there will be a period of delay before the operation of Delay 2. Delay 1 can be varied from 0.04 to 2.0 sec., and represents the interval between the triggering signal and the beginning of unblanking, determined by Delay 2. When Delay 2 is activated, it sends a signal to the signal amplifier of the dissector. The duration of this signal can be varied from 0.03 to 0.74 sec. The dissector signal amplifier can be adjusted so that when activated the amplitude of a timing signal applied to the Z axis of the cathode ray oscillograph for the duration of Delay 2 may be increased (unblanked) or decreased (blanked). With decreased amplitude, the beam becomes less intense. The latter technique of selective blanking is valuable in dimming the beam when the signal is of long duration, as during the inscription of the ST-T loop. In actual practice, selective unblanking has been more practical, i.e., the oscilloscope beam is extinguished except during the period of unblanking.

The timing signal, which will be described later, causes the beam of the oscillograph to be interrupted periodically. The output of Delay 2 is also applied to a solenoid circuit whereby a relay is closed during the blanking or unblanking period. This relay can be used to activate external circuits such as inserting signals into a direct-writing electrocardiograph to indicate the start and duration of blanking or unblanking. The solenoid circuit has been used to close the standardization circuit of a single-channel direct-writing electrocardiograph during the period of dissection. This technique furnishes a simultaneous record of the dissected portion of the QRS-T loop and obviates the need for multiple-channel recorders.

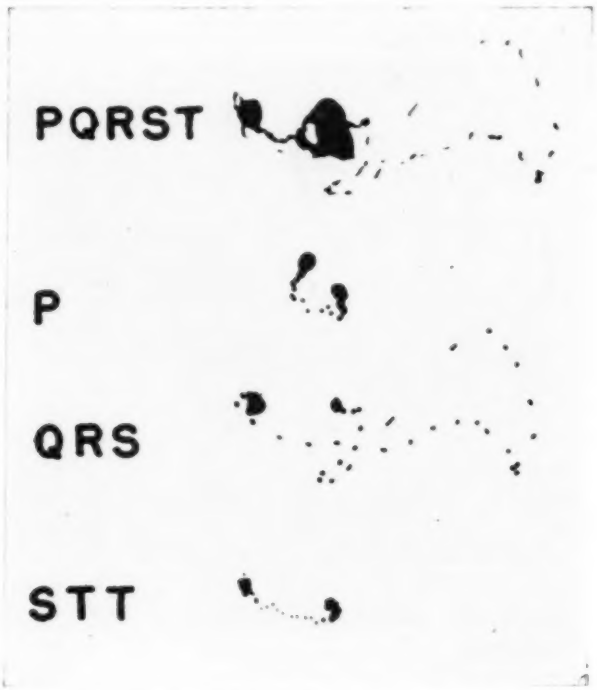

Fig. 3.—Complex vectorcardiogram of the sagittal plane, unraveled by selective unblanking. The patient has an interatrial septal defect, marked right ventricular hypertension and hypertrophy, and delayed right intraventricular conduction. The top row is the vectorcardiogram of *PQRST*. The *P* loop is open and has a counterclockwise rotation. The *QRS* loop begins from the open end of the *P* loop. The *QRS* loop is complex, having an initial clockwise direction, a brief period of counterclockwise rotation, and a final clockwise rotation. The QRS loop is open. The *ST-T* loop has a counterclockwise rotation.

At the end of its operation, Delay 2 sends a pulse to Delay 3, which is also variable. At the end of its operation, Delay 3 sends a pulse to the exposure switch. If the exposure switch is in its "off" position, this pulse is permitted to reset the flipflop switch which in turn resets the wave shaper. With such resetting, the dissector is now ready to be tripped again by a signal from the signal selector. If the exposure switch is in its "on" position, only one heart cycle or dissected portion is allowed to be blanked or unblanked, and thereby multiple exposures are prevented. In this "on" position, the reset switch is then used to reset the circuits manually.

A diagram of the time sequence operation of the selective dissector is shown in Fig. 2. Isolation of any loop can thus be obtained by two methods: (1) by intensifying the beam only during the inscription of the desired loop (unblanking), or (2) by dimming the beam during that part of the heart cycle when the desired loop is not being inscribed (blanking).

Timing Circuit.—The timing circuit is completely electronic and consists of a simple multivibrator synchronized to suitable multiples of the line frequency. The multivibrator's output is

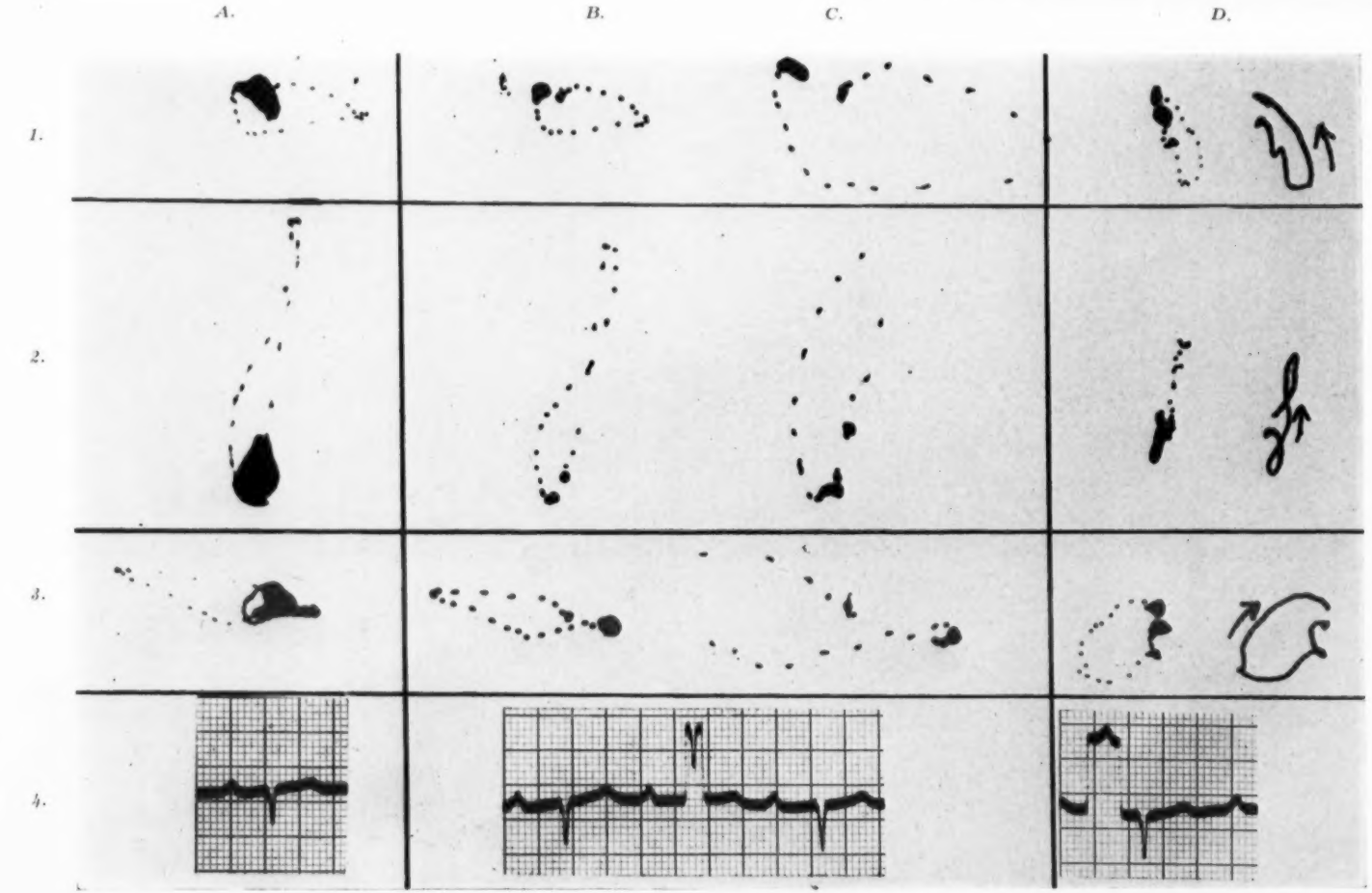

Fig. 4.—Partial dissection of vectorcardiogram of a patient with old posterior and anteroseptal infarcts to demonstrate the details of the initial portion of the QRS loop. Rows *1*, *2*, and *3* represent frontal, horizontal, and sagittal planes, respectively. Row *4* indicates the period of unblanking of the beam. Standardization is 1 millivolt equals 3 inches deflection in *A* and *B*, and 6 inches deflection in *C*. *A*, Vectorcardiogram of PQRST; *B*, Vectorcardiogram of QRS; *C*, Initial and terminal portions of QRS loops. Note clockwise rotation of QRS in frontal plane, counterclockwise rotation in the sagittal plane, and clockwise rotation of the initial half of the QRS in the horizontal plane with counterclockwise rotation of the terminal portion.

a distorted square wave, so that when it is applied to the Z axis of the oscillograph, the individual segments have a direction, i.e., are comet-shaped, indicating the direction of the movement of the beam. The direction of inscription of slowly moving loops (P and ST-T), however, is not clearly demarcated. The timing circuit operates independently of the blanking-unblanking circuit.

Oscillograph.—As mentioned previously, the oscillograph is a standard commercial unit (Dumont 279). Blanking or unblanking of the beam was obtained simply by adjusting the intensity control of the cathode-ray oscilloscope and the amplitude of the signal from the dissector. During the period of unblanking, the intensity of the signal from the dissector is increased, selectively illuminating that portion of the heart cycle; during the period of blanking, the intensity of the signal from the dissector is decreased, dimming or extinguishing that portion of the heart cycle.

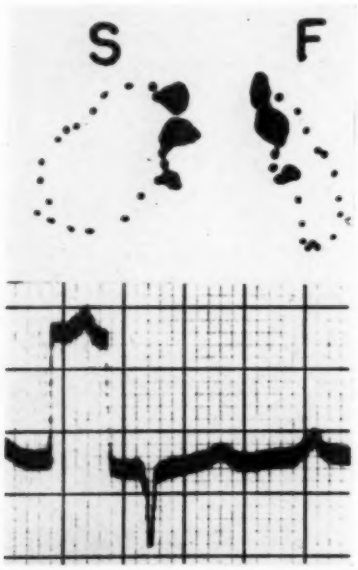

Fig. 5.—P loops of same patient of Fig. 4, showing left atrial hypertrophy. The P loops are open, showing clockwise rotation in the sagittal plane and counterclockwise rotation in the frontal plane.

Amplifiers.—There are three, three-stage differential push-pull A. C. voltage amplifiers* with self-balancing high-impedance input and phase-inversion output to permit single ending. There is a flat-frequency response from 0.5 c.p.s. to 500 c.p.s. The noise level is below 10 microvolts referred to input level.

Camera.—An ordinary 35 mm. camera (Dumont 296) and special Polaroid Land Camera (Dumont 297) have been used satisfactorily. Although provisions have been made for the use of an electric solenoid, these cameras have been controlled manually. By adjusting Delay 3 of the dissector, the beam may be unblanked for any desired submultiple of the heart beat, thus facilitating manual control of the camera shutter and avoiding double exposure.

DISCUSSION

With the usual technique of vectorcardiography, major emphasis has been placed on the analysis of the QRS loop. The paucity of reports on the ST-T and P loops confirms the inadequacy of the current methods of recording. In their original report, Wilson and Johnston[1] noted that the ". . . movements of the spot which represent the P and T waves are very small and their details are lost in the uniformly black area which surrounds the isoelectric point." A study of many published records since then, obtained with conventional vectorcardiog-

*Buffington Electronic Co., Cleveland, Ohio.

raphy, indicates that definition of the characteristics of the ST-T and P loops has been fraught with error and has remained in the domain of intuition or guess.

The technique of selective (differential) vectorcardiography makes possible a systematic study of the component loops of the heart cycle, especially analysis of complex loops, study of the P and ST-T loops, and of the details of the initial and terminal parts of the QRS loop (Figs. 3 to 9). By the use of the technique of partial dissection of each loop, it is possible to determine exactly which portion

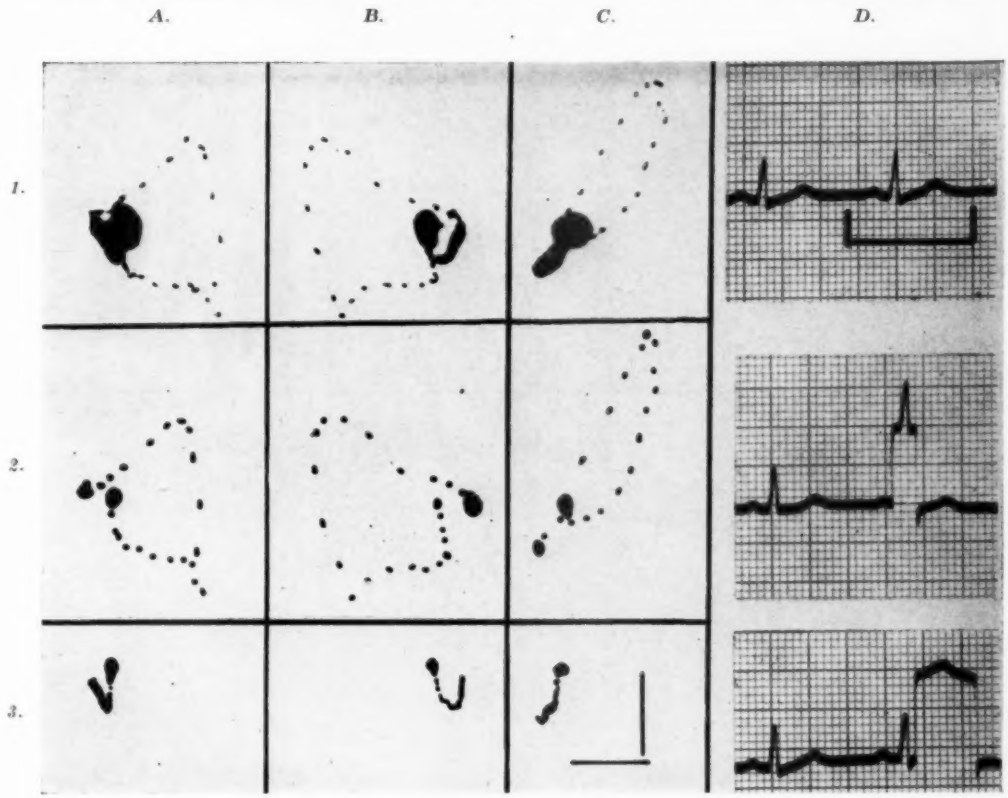

Fig. 6.—Selective unblanking of vectorcardiogram of patient with lateral infarct. *A*, *B*, and *C* represent frontal, sagittal, and horizontal planes, respectively. *D* represents the period of unblanking. Row *1*, Vectorcardiogram of PQRST; Row *2*, Vectorcardiogram of QRS, showing counterclockwise rotation in frontal and horizontal planes and clockwise rotation in the sagittal plane. The loops are open. In the horizontal plane, note the initial portion is directed anteriorly. In Fig. 5 this portion is absent, characteristic of anteroseptal infarction. The initial 0.03 sec. portion of the vectorcardiogram of the frontal plane is directed away from the left arm, producing and corresponding to a broad Q wave in VL. Row *3*, Vectorcardiogram of ST-T complex, showing the same rotation as the respective QRS loops. Note the early slow movement of the ST-T loop and the more rapid terminal movement. The standardization was 1 millivolt equalled 3 inches deflection. In the lower right hand corner of *C*, one-inch deflection on the X and Y axes is represented. The tracings are interrupted every 0.0033 sec.

of the electrocardiogram corresponds to which part of the vectorcardiogram (Fig. 9). Isolation of the various loops permits the estimation of the spatial areas for the further clarification of the spatial ventricular gradient.

Several examples of differential vectorcardiograms, presented in Figs. 3 to 9, illustrate details of component loops. For purposes of clarity, the photographs

have been reversed, but otherwise not altered. The reference system employed was that of Duchosal, as modified by Grishman.

There are other possible applications of our apparatus. For example, the present apparatus can be readily adapted to control the exposure of roentgeno-

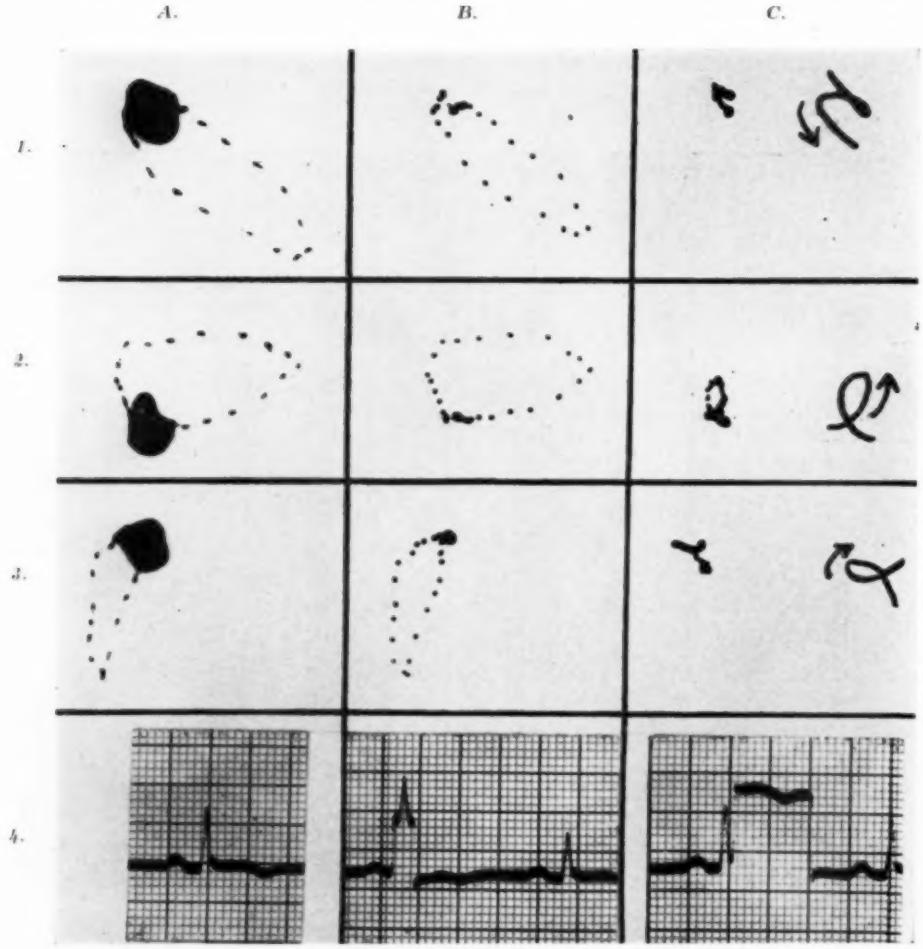

Fig. 7.—Dissection of vectorcardiograms of patient with anteroseptal infarct in the negative T stage. Rows *1*, *2*, *3*, represent frontal, horizontal, and sagittal planes, respectively. Row *4* indicates the duration of unblanking. *A*, Vectorcardiogram of PQRST; B, Vectorcardiogram of QRS. Note clockwise rotation of frontal and sagittal planes, and counterclockwise rotation of horizontal plane. The initial portion of the QRS loop in the horizontal plane is flattened, characteristic of anteroseptal infarction. *C* shows counterclockwise rotation of the T loop in the horizontal plane, and complex T loops in the other two planes, the latter showing clockwise rotation of the initial portion and counterclockwise rotation of the terminal portion. Tracings are interrupted every 0.0033 sec.

Fig. 8.—Dissection of vectorcardiogram of patient with left bundle branch block and recent anterior infarction. Rows *1*, *2*, and *3* represent frontal, horizontal, and sagittal planes, respectively. In row *4* the period of unblanking is indicated by the elevation of the electrocardiographic base line. Details of the P, QRS, and ST-T loops are shown in *B*, *C*, and *D*, respectively. Vectorcardiogram of QRS shows clockwise rotation in the horizontal and sagittal planes, and counterclockwise rotation in the frontal plane. The QRS loops are open, indicating S-T junction deviation. The first portion of the ST-T loop moves slowly posteriorly, from right to left, the second portion moves downward about 85 degrees, and the terminal portion moves more rapidly leftward and toward the back. The P loops are open and show counterclockwise rotation in the frontal plane and clockwise rotation in the horizontal and sagittal planes. Tracings are interrupted every 0.0033 sec.

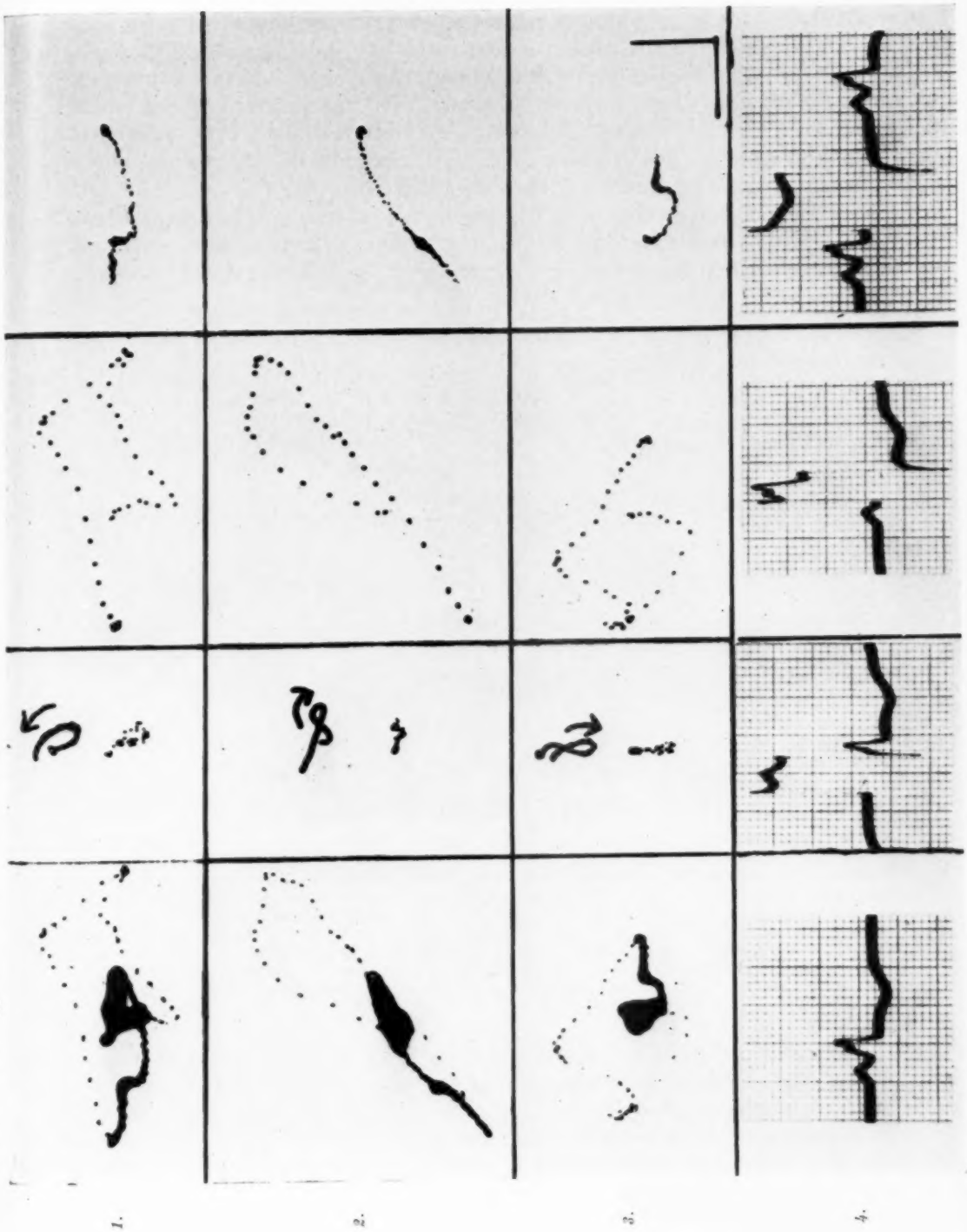

Fig. 8.—*For legend see opposite page.*

grams during any desired portion of the heart cycle, to calculate stroke volume, or to correlate electrical and mechanical events during angiocardiography.

The present selective dissector apparatus has the following advantages: (1) this apparatus can be used with commercially available cathode-ray oscilloscopes, preamplifiers, and ordinary cameras. Simultaneous records can be obtained on a standard electrocardiogram with clear marking of the blanked or unblanked portion. (2) The use of the QRS spike as the trip voltage allows for a better signal-to-noise ratio than does the use of the P wave. The QRS complex is more dependable as a tripping signal, especially in patients with no P waves, low P waves, retrograde P waves, auricular fibrillation or flutter, and in patients with extracardiac (somatic) tremors. (3) The assembled apparatus has been rack mounted and is portable.

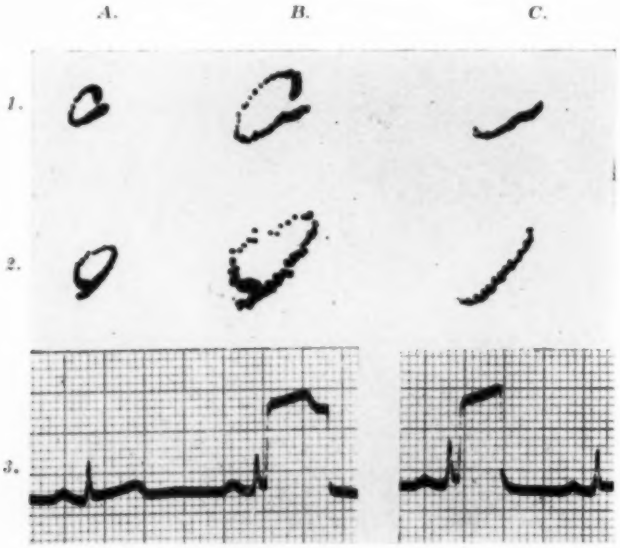

Fig. 9.—Vectorcardiogram of the ST-T complex showing the corresponding portions of the vectorcardiogram and electrocardiogram. Row *1* represents vectorcardiogram of ST-T complex of the sagittal plane; Row *2*, Vectorcardiogram of ST-T of horizontal plane. Row *3*, Electrocardiogram showing duration of unblanking. In *A* standardization is 1 millivolt equals 3 inches deflection; in *B* and *C* standardization is 1 millivolt equals 6 inches deflection. Note the direction of rotation is clockwise in the sagittal plane and counterclockwise in the horizontal plane. In *C* partial dissection of the ST-T loop shows that the slow first half of the ST-T loop ends at the apex of the T wave in the electrocardiogram in Row *3*. The descending limb of the T wave corresponds to the more rapidly moving second half of the ST-T loop.

There are several disadvantages in using QRS as the triggering signal. In patients with extreme sinus arrhythmia, the variations from beat to beat may make it difficult to blank or unblank selectively the following QRS complex. By increasing the duration of the dissecting signal, the first QRS complex following the triggering QRS may be "targeted in" similar to the practice in artillery fire: thus if the variation from beat to beat is 0.12 sec., and the duration of QRS is 0.11 sec., if the beam is unblanked for 0.23 sec., a QRS complex will be embraced during the unblanking. In actual practice, selective unblanking has

not been a major problem. On the other hand, isolation of the ST-T loop presents no difficulty whatsoever in any arrhythmia, since its QRS complex is used to trigger the dissector.

SUMMARY

A practical selective dissector apparatus has been constructed and has been used with commercially available equipment to separate and record the component loops of the vectorcardiogram (P, QRS, ST-T loops).

REFERENCES

1. Wilson, F. N., and Johnston, F. D.: The Vectorcardiogram, Am. Heart J. **16**:14, 1938.
2. Donzelot, E., Milovanovich, J. B., and Kaufmann, H.: Etudes Pratiques De Vectorgraphie, L'Expansion Scientifique Francaise, 1950.
3. Briller, S. A., Marchand, N., and Kossmann, C. E.: A Differential Vectorcardiograph, Rev. Scient. Instruments **21**:805, 1950.
4. Misao, T., Kimura, N., and Yoshida, T.: Research on Vectorcardiography. Twenty-second Report. Research Especially on the Method of Inscription, Nippon J. Angiocardiology **13**:118, 1949.

ACETYL-DIGITOXIN

Clinical Observations on the Treatment of Patients With Advanced Congestive Heart Failure

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IN THE treatment of cardiac failure pure glycosides have two main advantages: their effect is constant, and their dose can be assessed gravimetrically. Because of differences between the various compounds, in absorption as well as in speed, intensity, and duration of action, the most suitable preparation has to be selected in every case. Digitoxin, the first glycoside to be isolated by Nativelle[17] from *Digitalis purpurea* in crystalline form, is still widely used, despite its disadvantage of causing frequent and persistent toxic side effects, which are due to pronounced cumulation resulting from the slow dissipation of the glycoside. It has thus been stated by several authors that, for routine treatment, digitoxin is not the glycoside of choice (DeGraff and associates,[6] Diefenbach and Meneely[7]).

In an attempt to find a compound with digitoxin-like effects, but having a greater therapeutic margin, Stoll and Kreis[20] prepared from *Digitalis lanata* a new glycoside, acetyl-digitoxin-α, which is formed from lanatoside A by enzymatic cleavage of one molecule of glucose. Pharmacologic analysis of this compound by Rothlin and associates[19] showed that, like digitoxin, it is well absorbed from the intestinal tract and greatly reduces the heart rate, but at the same time is less toxic. These properties are of considerable clinical interest, and we have therefore tested acetyl-digitoxin (AD) extensively in our hospital for the last eighteen months,[14] with special reference to the following points.

1. Dosage: (a) Digitalization dose
   (b) Maintenance dose
2. Therapeutic margin:
   (a) Maximum dose, and overdosage
   (b) Smallest maintenance dose giving rise to toxic side effects
3. Clinical and pharmacological characteristics:
   (a) Absorption
   (b) Latent period
   (c) Duration of effect
   (d) Dissipation and rate of elimination
4. Therapeutic action on heart and pulse rate, blood pressure, size of heart, diuresis, body weight, symptoms and signs of congestion, vital capacity, venous pressure, circulation time, general condition, and electrocardiogram
5. Side effects
6. Range of indications
7. Comparison with other cardiac glycosides

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METHOD

The general therapeutic management consisted of rest in bed, restriction in the intake of salt, and restriction of fluid intake to 1,000 to 1,500 ml. If required, aminophylline, oxygen, analeptic drugs, and opiates were given. When the patient's condition had become stationary, we started treatment with acetyl-digitoxin, given orally or intravenously, usually with an initial loading dose. Either one single digitalizing dose was administered in accordance with Gold and associates,[10] or repeated smaller doses were given until digitalization was reached in the course of two to three days. Once compensation was achieved it was maintained with the minimum maintenance dose. In order to assess the therapeutic margin, we gave a few patients additional doses of acetyl-digitoxin at regular intervals after the full glycoside effect had become established, and thus determined the minimum toxic dose. Mercurial diuretics preceded by acidifying salts were used only in patients in whom the glycoside failed to eliminate edema completely. In such cases sodium-ion exchange resins were also employed occasionally.

The effect of the glycoside was judged by the clinical picture, with daily checks of pulse rate, pulse deficit, blood pressure, respiratory rate, diuresis, body weight, and signs of congestion, also by repeated measurements of heart size (teleradiograms, orthodiagrams, determination of the heart volume after Kjelberg and associates[11]), vital capacity, venous pressure, and circulation time.

Venous pressure was measured by the method of Moritz and Tabora[16] (direct method, the manometer being connected to a needle inserted into the right antecubital vein with the patient in the recumbent position); values of 1 to 9 cm. H_2O were considered as normal.

Circulation time was measured with an oximeter applied to the right ear. The lung-to-ear circulation time was determined as the interval between the beginning of a deep and quick inspiration of N_2O and the first deflection of the galvanometer caused by the arrival of anoxemic blood in the ear. Similarly, the arm-to-ear circulation time was measured by injecting 3 to 4 ml. of a 1 per cent solution of Evans blue or methylene blue into the right antecubital vein and

TABLE I. NORMAL CIRCULATION TIME IN SECONDS (PHOTOELECTRIC DETERMINATION WITH AN OXIMETER)

	LUNG-TO-EAR	ARM-TO-EAR	ARM-TO-LUNG
Own determinations	5.5 (4.4–6.9)	11.5 (7.3–16.5)	6.2 (2.5–10.0)
Matthes[15]	4.0 (3.0–5.5)	10.7 (8–13)	6.7 (5–9)
Lindgren[13]	5.6 (4.0–6.8)	10.7 (8–17.7)	
Knutson et al.[12]	4.7 ± 0.3 (3.0–6.8)	13.4 ± 1.0 (10–20)	
Wexler and Whittenberger[21]	5.2 (4.1–7.0)		
Callebaut et al.[3]	5.1 (3.7–7)	10.3 (7–16.5)	

photoelectric recording of the moment at which the dye arrived in the vessels of the right ear. The arm-to-lung circulation time was calculated by subtracting the lung-to-ear time from the arm-to-ear time. In Table I, our normal values are listed, obtained in thirty individuals between 20 and 60 years of age with normal cardiovascular systems; for comparison the results of other authors obtained by similar methods are also given. For further particulars of the methods, see Forster and Lottenbach.[8]

RESULTS

Our investigations were carried out on 120 hospitalized patients, all suffering from an advanced degree of cardiac failure of varying etiology. Two-thirds were over 60 years of age. Seventy-five per cent had one or several complications, such as thrombosis, pulmonary infarction, pneumonia, apoplexy, or cirrhosis of the liver.

1. *Determination of the Effective Dosage.—*

Initial dose: The dose of the glycoside necessary for complete digitalization varies according to the time during which it is desired to achieve it. In accordance with the degree of decompensation and of the tachycardia, the method was varied, thus: (a) the dose necessary for full digitalization was given within 24 hours, either as one single dose of acetyl-digitoxin (after Gold[10]) or in two or three divided doses; (b) digitalization was carried out in the course of two to three days by repeatedly giving smaller doses of the glycoside at intervals of 6 to 8 hours; (c) in certain cases with bradycardia treatment was carried out with small daily doses, the dosage being gradually increased.

Patients with auricular fibrillation and high ventricular rate lend themselves particularly well to studies on the relations between dosage and time required for full digitalization. In cases of this kind, patients are considered fully digitalized when the ventricular rate is reduced to 70-75 per minute and the pulse deficit is abolished. The results of these investigations are presented in Table II.

TABLE II

DIGITALIZATION WITHIN (DAYS)	AVERAGE DOSE (MG.)	DOSE RANGE (MG.)	NO. CASES
Digitalizing dosage of acetyl-digitoxin given by mouth			
1	2.4	2.0 – 3.0	17
2	2.8	2.4 – 3.6	10
3	3.4	2.8 – 6.0	26
4	4.0	3.8 – 4.4	7
Digitalizing dosage of acetyl-digitoxin given intravenously			
1	1.5	1.3 – 2.0	9
2	1.8	1.6 – 2.2	9
3	1.9	1.4 – 2.4	10
4	2.6	2.0 – 3.4	7

Maintenance dose: Once compensation was achieved it was maintained by the minimum daily single dose, given orally as a rule, but in advanced cases given intravenously for a few days.

The maintenance dose varied widely in different cases. Given intravenously it was 0.2 mg. on an average (0.1 to 0.4 mg.), given orally 0.1 to 0.4 mg., usually 0.2 to 0.3 mg. Only in rare cases was it necessary to increase the daily dose to 0.6 mg. in order to prevent the recurrence of cardiac failure.

2. *Therapeutic Margin.*—

The hazards of treatment with cardiac glycosides are largely determined by the therapeutic margin of the preparation used. This is therefore a decisive factor in the use of a glycoside in hospitals and particularly in general practice. The therapeutic margin, however, depends only partially on the nature of the compound, as it is also determined by the susceptibility of the individual patient to the cardiac glycosides. The susceptibility depends essentially on the etiology and degree of cardiac failure, on the cardiac reserve, and on extracardiac factors, such as the protein, potassium, and calcium content of the blood, hepatic and renal function, and basal metabolic rate. The therapeutic margin thus varies greatly in individual cases.

With rapid oral digitalization, carried out within one or three days, the therapeutic margin can be determined in the following way. The dose of the glycoside necessary for rapid digitalization is divided into small, single doses and these are given at regular intervals for several consecutive days. The dose which is necessary to achieve compensation by digitalization is determined, as well as the dose of the glycoside which just produces toxic manifestations. When the administration of 2.4 mg., the dose required for achieving full digitalization within 24 hours, was continued, the minimum toxic dose in five cases was found to be 5.6 mg. on an average (4.8 to 7.5 mg.). Thus, the therapeutic dose was on an average 53 per cent of the minimum toxic dose. With smaller daily oral doses (1.2 to 1.8 mg.), this figure varied between 40 and 60 per cent.

With an initial oral dose of 2.4 mg. the full effect was observed after 24 hours; if the administration of the glycoside was continued at the same dosage level, the first toxic manifestations appeared on the third day. With a daily dose of 1.2 mg. acetyl-digitoxin, compensation was as a rule achieved after three days while toxic effects occurred only after five to six days.

If 0.8 mg. was given daily by the intravenous route, the digitalizing dose of 1.6 to 2.4 mg. was, on an average, 65 per cent of the toxic dose (2.8 to 6.4 mg.).

During maintenance treatment, the therapeutic margin was ascertained by determining the smallest dose which, if given daily, maintained compensation of the circulation, as well as the dose of the glycoside precipitating the first signs of intoxication.

In our investigations, the minimum toxic maintenance dose varied between 0.3 and 0.8 mg. daily, the average being 0.6 mg., that is, well above twice the average therapeutic maintenance dose.

3. *Clinical and Pharmacologic Characteristics.*—

Absorption: According to DeGraff and associates[5,6] and Oettel,[18] it is possible to calculate the absorption ratio by comparing the intravenous and oral daily doses necessary for maintaining compensation. The average figures for acetyl-digitoxin, obtained from investigations in twenty-seven patients, were 0.2 and 0.3 mg., from which it can be concluded that the intestinal absorption is 67 per cent.

The *latent period* (the interval between administration and the first sign of a drug effect) can best be determined in patients with auricular fibrillation and high ventricular rate. Heart rate and pulse rate were recorded regularly at short intervals. A glycoside effect can be assumed to have begun at the time when the heart rate has decreased by 10 per cent below the initial figure. For acetyl-digitoxin this latent period measures 20 to 30 minutes when injected intravenously (Fig. 1), and 2 to 4 hours when given orally.

The *duration of effect* is ascertained by interrupting treatment after rapid complete digitalization and determining the time required for the heart rate to rise again to 90, or for a pulse deficit to reappear. Ten patients were investigated in this way and the duration of the effect of acetyl-digitoxin was found to be on an average 9 (4 to 14) days.

Dissipation: The rate of elimination, that is, the ratio between the intravenous maintenance and intravenous digitalizing dose, indicates the fraction of the amount of glycoside present in the body, which is daily broken down or excreted. Twenty-two patients were investigated in

this way and an average rate of elimination of 14 per cent acetyl-digitoxin was found. Table III lists the corresponding figures for several cardiac glycosides in common use.

TABLE III. RATE OF ELIMINATION OF THE MOST COMMONLY USED CARDIAC GLYCOSIDES

GLYCOSIDE	I.V. MAINTENANCE DOSE (MG.)	I.V. DIGITALIZING DOSE (MG.)	RATIO	PER CENT ELIMINATED
1. Strophosid	0.25	0.5	1:2	50
2. Cedilanid	0.4	2.0	1:5	20
3. Digilanid	0.4	2.0	1:5	20
4. Acetyl-digitoxin	0.2	1.5	1:7	14
5. Digitoxin	0.15	2.0	1:14	7

The greater the fixation of the cardiac glycoside, the smaller the amount eliminated (1, 2, and 5' according to Augsberger[1]; 3 and 4, according to own observations).

4. *Therapeutic Effects.*—

The *heart rate* is considerably reduced by acetyl-digitoxin. In cases of auricular fibrillation with high ventricular rate, an intravenous injection of 1.4 to 1.6 mg. acetyl-digitoxin reduces the heart rate to 70 per minute, with concomitant disappearance of a pulse deficit in four hours at the earliest (Fig. 1) and in 48 hours at the latest. In sinus tachycardia the normal rate was restored within 4 to 6 days in 60 per cent of the cases. In patients with normal or slow ventricular rate the reduction in rate was less marked so that on several occasions such patients could be treated by small doses of acetyl-digitoxin given orally.

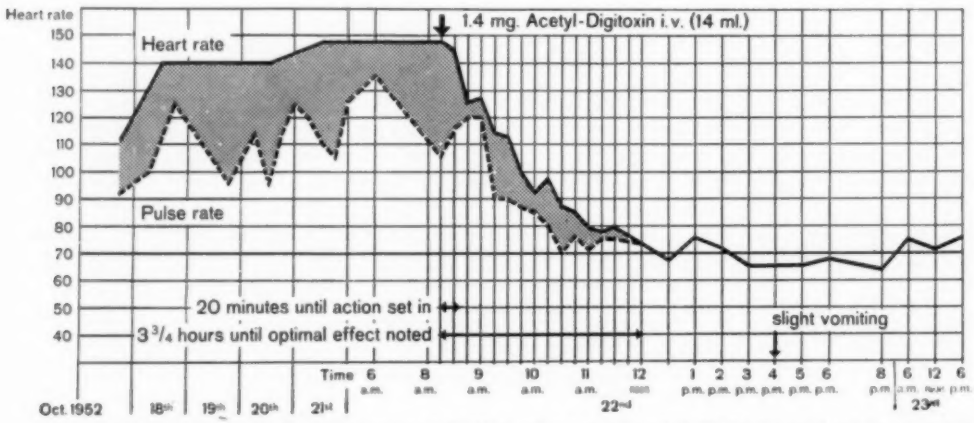

Fig. 1.—Effect of a single intravenous injection of 1.4 mg. acetyl-digitoxin on heart and pulse rate in a 57-year-old woman with rheumatic mitral stenosis and insufficiency, auricular fibrillation with high ventricular rate, pulmonary and hepatic congestion, and extensive edema.

Effect on cardiac rhythm: On admission, fifty-five patients had sinus rhythm which, in three instances, changed into auricular fibrillation during treatment. Sinus rhythm was restored in three of fifty-seven cases of auricular fibrillation. Seven patients had auricular flutter; in five of these, conversion to sinus rhythm could be achieved by large doses of acetyl-digitoxin given intravenously or by mouth. In one woman with paroxysmal supraventricular tachycardia, a sudden transition to sinus rhythm took place five minutes after the intravenous injection of 1.0 mg. acetyl-digitoxin.

The *positive inotropic effect* of a cardiac glycoside can be assessed clinically only indirectly. We therefore resorted to animal experiments. In anesthetized cats the blood pressure and pulse pressure in the carotid artery were investigated before and after the intravenous injection of 0.03 mg./kg. acetyl-digitoxin; arterial resistance was varied by means of a cuff applied around

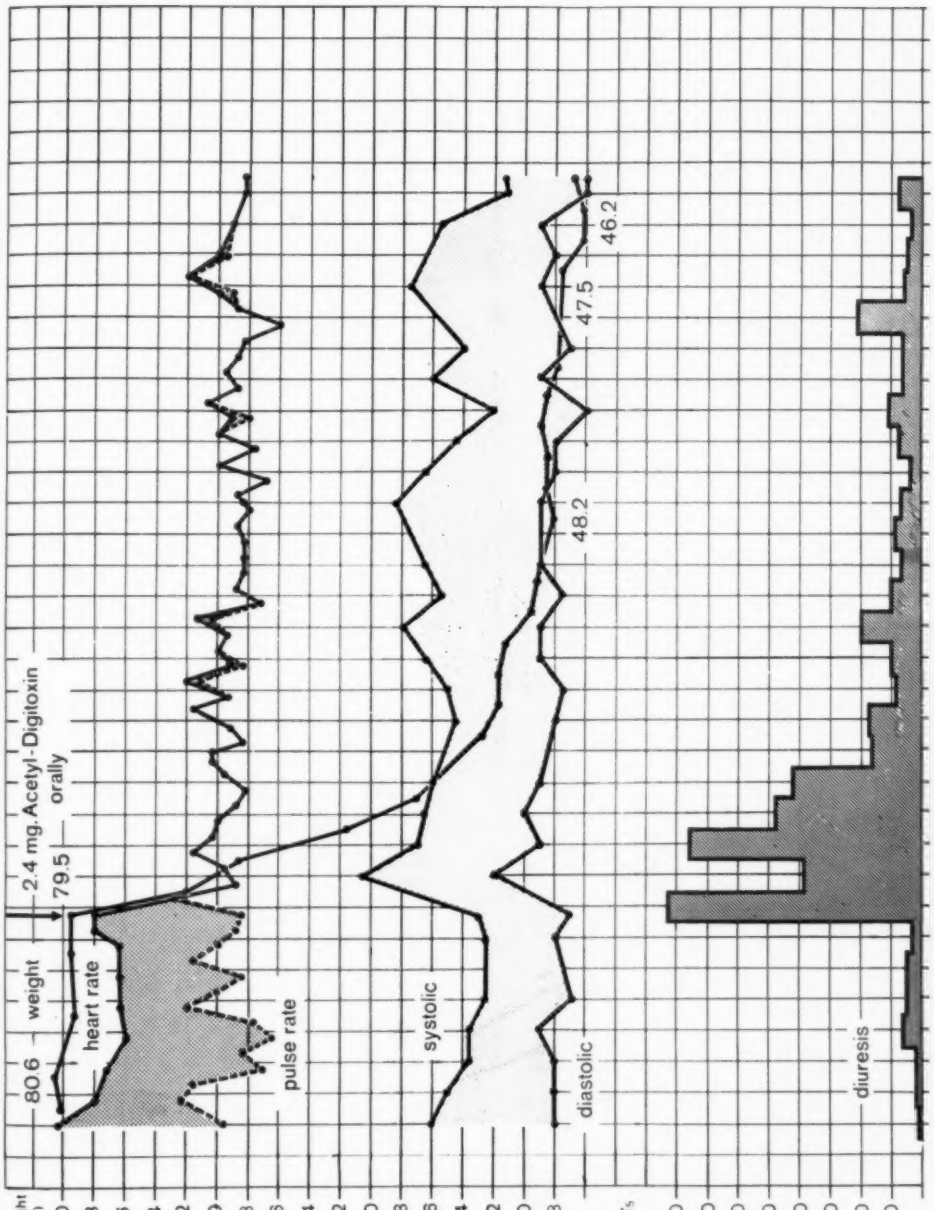

Fig. 2.—Effect of a single oral dose of 2.4 mg. acetyl-digitoxin in a 65-year-old woman with mitral insufficiency, auricular fibrillation with high ventricular rate, and generalized dropsy: lowering of pulse rate, rise in systolic blood pressure associated with increase in pulse pressure and marked increase in diuresis. Reduction of weight by 34 kg. within three weeks. Although treatment with the glycoside was discontinued for 22 days, compensation was maintained. Subsequently, prolonged treatment with a maintenance dose of 0.3 mg. acetyl-digitoxin given by mouth.

TABLE IV. EFFECT OF TREATMENT WITH ACETYL-DIGITOXIN ON VENOUS PRESSURE, CIRCULATION TIME, AND VITAL CAPACITY IN PATIENTS WITH HEART FAILURE

PATIENT AGE (YR.)	DIAGNOSIS	DATE 1952	TOTAL AMOUNT OF ACETYL-DIGITOXIN ADMINISTERED (MG.)	BODY WEIGHT (KG.)	PULSE RATE			BLOOD PRESSURE (MM. HG)	VENOUS PRESSURE (MM. H_2O)	CIRCULATION TIME			VITAL CAPACITY (ML.)
					HEART	RADIAL ARTERY	DEFICIT			ARM-TO-EAR (SEC.)	LUNG-TO-EAR (SEC.)	ARM-TO-LUNG (SEC.)	
1. W.H. 55 ♂	Myocardial degeneration; heart failure; bronchial asthma; sinus rhythm	4-29	31.4	86.2	112	112	0	170/125	200	44	13.2	30.8	1500
		5-16		74.7	96	96	0	145/100			9.5		
		6-27		78.0	100	100	0	145/95	19	20.5	10.3	10.2	2980
2. P.S. 48 ♂	Myocard. degenerat. heart failure, chronic myocarditis?, auricular fibrillation with rapid heart rate, pulmonary edema	5-24	16.0	94.6	132	92	40	130/80	180	29.8	16.3	13.5	1800
		5-26		93.3	84	72	12	130/80	60	31.0	12.6	18.4	
		5-30		89	80	56	24	130/80	102	25			3070
		6-6		86.7	92	56	36	120/80	93				3000
		6-14		87.3	84	60	24	120/60	110	27.5	12.1	15.4	3200
		7-5		88.5	74	62	12	155/75	55	19.5	10.2	9.3	4700
3. E.H. 44 ♂	Mitral stenosis and insufficiency, auricular fibrillation, condition after sepsis lenta	3-19	12.2	65	98	90	8	160/110	115	14.5	12.7	1.8	1700
		4-25		64.8	60	60	0	135/75	86	15.5	11.3	4.2	2800
4. M.Sch. 53 ♀	Mitral stenosis and insufficiency, aortic insufficiency, auricular fibrillation with rapid heart rate	6-12	27.6	68.3	144	110	34	155/80	60	16.0	10.1	5.9	1200
		7-18		65.5	76	76	0	160/80	86	13.9	8.3	5.6	2100
5. M.A. 74 ♀	Myocardial degen., heart failure, auricular fibrillation with rapid heart rate	5-17	21.4	52.6	120	120	0	100/60	40	28	11.4	16.6	1200
		6-26		94.8	80	80	0	150/70	45	15	9.0	6.0	1300
6. H.Sch. 57 ♀	Mitral stenosis and insufficiency, auricular fibrillation with rapid heart rate	10-18	13.5	65.8	132	100	32	140/80	110	20.3	11.3	9.0	1770
		11-1			94	88	6	160/90	130	26.8	10.5	16.8	1350
		12-13		55.5	64	64	0	125/80	63	17.0	11.4	5.6	1780
7. L.S. 56 ♀	Myocardial degen., heart failure, auricular fibrillation with rapid heart rate	10-21	3.4	60.7	186	112	74	130/90	169	17.5	11.5	6.0	850
		11-1		53.8	100	86	14	130/70	24	12.0	8.0	4.0	1730

1–7 cases of heart failure before, during and after treatment with acetyl-digitoxin. Patients number 3 to 5 were suffering primarily from failure of the left side of the heart, the others had combined left and right failure.

the abdominal aorta. Before the injection of acetyl-digitoxin, increasing the pressure in the cuff by 50, 100, and 150 mm. Hg resulted in an insignificant rise of systolic and diastolic pressure in the carotid without any change in pulse pressure. After the injection of acetyl-digitoxin, on the other hand, the same increase in resistance was followed by an increase in pulse pressure as well as by a distinct persistent increase in systolic and diastolic pressures, signifying an improvement by acetyl digitoxin of the adaptability of the heart to increased demand.

Clinically, acetyl-digitoxin usually raises the systolic pressure and pulse pressure in cases of low blood pressure due to cardiac failure. In the majority of cases the diastolic pressure decreases and in cases of hypertension due to congestion the blood pressure is restored to normal. Detailed figures are contained in the paper by Löffler and associates.[14] These changes in blood pressure suggest that the drug increases cardiac efficiency to a notable degree.

Reduction in heart volume, indicating a decrease in the amount of residual blood, was often pronounced. Thus, in a 75-year-old man with congestive failure, aortic insufficiency and auricular fibrillation with slow ventricular rate, the heart volume (determined by the method of Kjelberg and associates[11]) decreased from 1,880 to 1,480 c.c. within one month of taking a total of 14.0 mg. acetyl-digitoxin by mouth, and concurrently the manifestations of congestive failure disappeared completely.

The *effect on diuresis* (Fig. 2) was investigated in the following way. Fluid intake was kept constant; the percentage increase in the average daily output during the first five days of treatment with the glycoside was compared with the data from a control period of at least three days during which no glycoside was administered, immediately prior to treatment with the glycoside. In forty-four patients, with no clinical signs of edema, acetyl-digitoxin given by mouth or intravenously, increased diuresis by approximately 20 per cent. In the presence of edema acetyl-digitoxin, given intravenously in eighteen cases and orally in nine, increased diuresis by 70 and 160 per cent, respectively.

After intravenous injection, diuresis attained its maximum on the second to fourth day; if given by mouth, on the third to fifth day in two-thirds of the cases, though in eight patients this occurred as early as the first or second day. In cases with auricular fibrillation this usually coincided with the time at which the pulse deficit was nearly eliminated and the heart rate correspondingly reduced.

The *signs of congestion* in the systemic and lesser circulations usually subsided rapidly in the course of acetyl-digitoxin treatment, and the patients' general condition improved concurrently.

In cases of left ventricular failure, dyspnea as well as the auscultatory and radiologic signs of pulmonary congestion became less marked. The relief in breathing which most patients felt as early as the second day of treatment was usually associated on the third day with a reduction of the respiratory rate and subsequently with a considerable increase in vital capacity (see Table IV).

In patients with right ventricular failure, edema, congestion of the liver, and transudates subsided, usually in this order. Large effusions were often tapped at an early stage, in order to shorten the duration of hospitalization. In fifteen patients with generalized dropsy, complete elimination of edema could only be achieved by repeated injections of mercurial diuretics, preceded by acidifying salts. In three instances the use of sodium-ion exchange resins was successful.

Venous pressure which, in patients with right ventricular failure, was raised up to 30 cm. H_2O dropped to normal usually within one week of treatment with the glycoside (Table IV).

The *circulation times*, arm-to-ear, arm-to-lung, and lung-to-ear, on admission were considerably increased, according to the severity of failure. They decreased as the circulation improved but became normal only in rare cases (Table IV). Despite restoration of compensation there is still an increased amount of residual blood in the ventricles and thus some dilatation persists which, according to Gernandt and Nylin[9], mainly determines the increase in circulation time.

The *electrocardiogram* showed the well known glycoside effects, such as shortening of the Q-T interval, distortion of the S-T segment with displacement in a direction opposite to that of the initial deflections, associated with flattening of the T wave. The following side effects were observed, some of them in instances in which excessive doses were given experimentally: ventricular extrasystoles (7 cases), bigeminal rhythm (9), lengthening of atrioventricular conduction

time including partial or complete atrioventricular block (2), and one case each of ventricular and supraventricular tachycardia. All these changes, including the more pronounced arrhythmias, were usually reversible within two to three days, if the glycoside was temporarily discontinued (though in some cases potassium chloride or Pronestyl had to be given in addition).

Therapeutic results: In 120 cases of advanced congestive heart failure treated with acetyl-digitoxin good or excellent results were obtained in 43 per cent and fair results in 38 per cent. The remaining 19 per cent were more or less resistant to therapy, of which 5 per cent were also not improved by other glycosides, such as Strophosid, ouabain, or lanatoside C.

5. *Side Effects.*—

In one-quarter of our patients certain toxic side effects were observed during the initial or maintenance stages of treatment. These did not differ from those produced by other digitalis glycosides. Apart from the changes in the electrocardiogram already referred to, they consisted in nausea and vomiting; in two patients visual disturbances were observed (blurring of vision and micropsia or colored vision), and in one case acute psychosis with delirium occurred. When treatment with acetyl-digitoxin was discontinued, they disappeared within one to three days.

To a certain extent such toxic manifestations are due to the fact that at first we had no clinical experience with acetyl-digitoxin and also that the initial dosages used were deliberately high in order to investigate the potency and toxicity of the drug. Subsequently, over a period of months when moderate dosages were used routinely to achieve digitalization within two to three days, and maintenance treatment was adjusted accordingly, side effects were rarely observed. This demonstrates that acetyl-digitoxin is well tolerated.

Since the drug is not readily soluble in water, it is necessary to add alcohol to the solution for injection, which may produce a burning sensation and cramplike pain in the vein used for injection. This can be avoided by diluting one part of the ampule solution with three parts of a 5 to 10 per cent solution of glucose or with aminophylline.

DISCUSSION

Acetyl-digitoxin* is a crystalline pure glycoside which has the full digitalis effect, and the dose of which can be assessed gravimetrically. It reduces the heart rate considerably, has an excellent diuretic effect, and is well absorbed from the intestinal tract, its rate of absorption being 67 per cent (Cedilanid 40 per cent, digitoxin 80 per cent). It increases cardiac efficiency (positive inotropic effect), which manifests itself clinically by raising an abnormally low blood pressure, increasing pulse pressure, and also frequently by reducing the heart size and thus the amount of residual blood. It acts relatively quickly, for example, 20 to 30 minutes after intravenous injection and 2 to 4 hours when given by mouth. Its effect lasts nine days and its rate of elimination is 14 per cent. These properties place acetyl-digitoxin midway between digitoxin and the glycosides Digilanid and lanatoside C.

Acetyl-digitoxin is characterized by being well tolerated and having a large therapeutic margin, thus combining the efficacy of digitoxin with the lower toxicity of the glycosides prepared from *Digitalis lanata*. Compared with digitoxin twice the amount of acetyl-digitoxin has to be given orally, for an identical effect to be produced. By the intravenous route 1.5 mg. acetyl-digitoxin and 1.2 mg. digitoxin are equivalent doses. However, as acetyl-digitoxin is well absorbed, treatment by mouth alone is often sufficient. Since the drug effect is more readily reversible than that of digitoxin, treatment is more easily controlled and toxic side effects, if they occur at all, subside more quickly.

*From Sandoz Pharmaceuticals, Hanover, N. J.

The primary indications for acetyl-digitoxin are all forms of cardiac failure associated with tachycardia, including cases with normal rhythm or arrhythmias, particularly auricular fibrillation with high ventricular rate, auricular flutter, and paroxysmal tachycardia. As far as patients with bradycardia are concerned, glycosides obtained from strophanthus and squill, having a less-marked effect on the vagus, or lanotoside C seem preferable, though we have successfully treated such cases with small doses of acetyl-digitoxin. The high rate of fixation of acetyl-digitoxin makes it generally very suitable for prolonged treatment of patients with chronic cardiac failure.

A dosage scheme for acetyl-digitoxin is as impracticable as with any other glycoside as the dosage has to be adjusted individually according to the patient's susceptibility which varies widely in different cases and to the type and severity of cardiac failure (Table V).

TABLE V. DOSAGE OF ACETYL-DIGITOXIN IN VARIOUS FORMS OF HEART FAILURE

	PAROXYSMAL TACHYCARDIA, AURICULAR FLUTTER, AURICULAR FIBRILLATION WITH HIGH VENTRICULAR RATE AND LARGE PULSE DEFICIT	OTHER FORMS OF HEART FAILURE WITH HIGH VENTRICULAR RATE (AURICULAR FIBRILLATION AND SINUS RHYTHM)	HEART FAILURE WITH LOW VENTRICULAR RATE
Rapid digitalization (within 24 hours)			
i.v. (1-2 injections)	1.5 mg. (1.3–2.0 mg.) = 15 ml. (13–20 ml.)		
oral		2.4 mg. (2.0–2.5 mg.)	
Slow digitalization (within 2-5 days)			
i.v. daily		0.8 mg. (8 ml.)	
total		1.9 mg. (1.6–2.4 mg.) = 19 ml. (16–24 ml.) within 2–3 days	
oral daily		1.2 mg.	0.8–1.2 mg.
total		2.8–3.6 mg. within 2–3 days	3.6–4.4 mg. within 3-5 days
Maintenance treatment			
i.v.		0.2 mg. (0.1 – 0.3 mg.) = 1 – 3 ml.	
oral		0.1 – 0.4 mg. (in rare cases 0.6 mg.)	

Rapid digitalization is indicated in patients with marked tachycardia in order to improve cardiac economy quickly; if possible this should be achieved within 24 hours by a dose of 2.0 to 2.4 mg. given by mouth, or 1.4 to 1.6 mg. by the intravenous route in one or two injections (provided that there has not been any prior treatment with a glycoside). In less urgent cases oral digitalization within 2 to 3 days is a milder method, best suited for routine treatment. It is carried out by giving several medium doses up to a maximum of 2.8 to 3.6 mg.

If the intravenous route is employed, a daily dose of 0.8 mg. is necessary, the total dose being 1.6 to 2.4 mg. Slow oral digitalization with small daily doses of 0.6 to 0.8 mg. is more suitable for patients with bradycardia. The initial digitalization is immediately followed by the maintenance treatment, the average

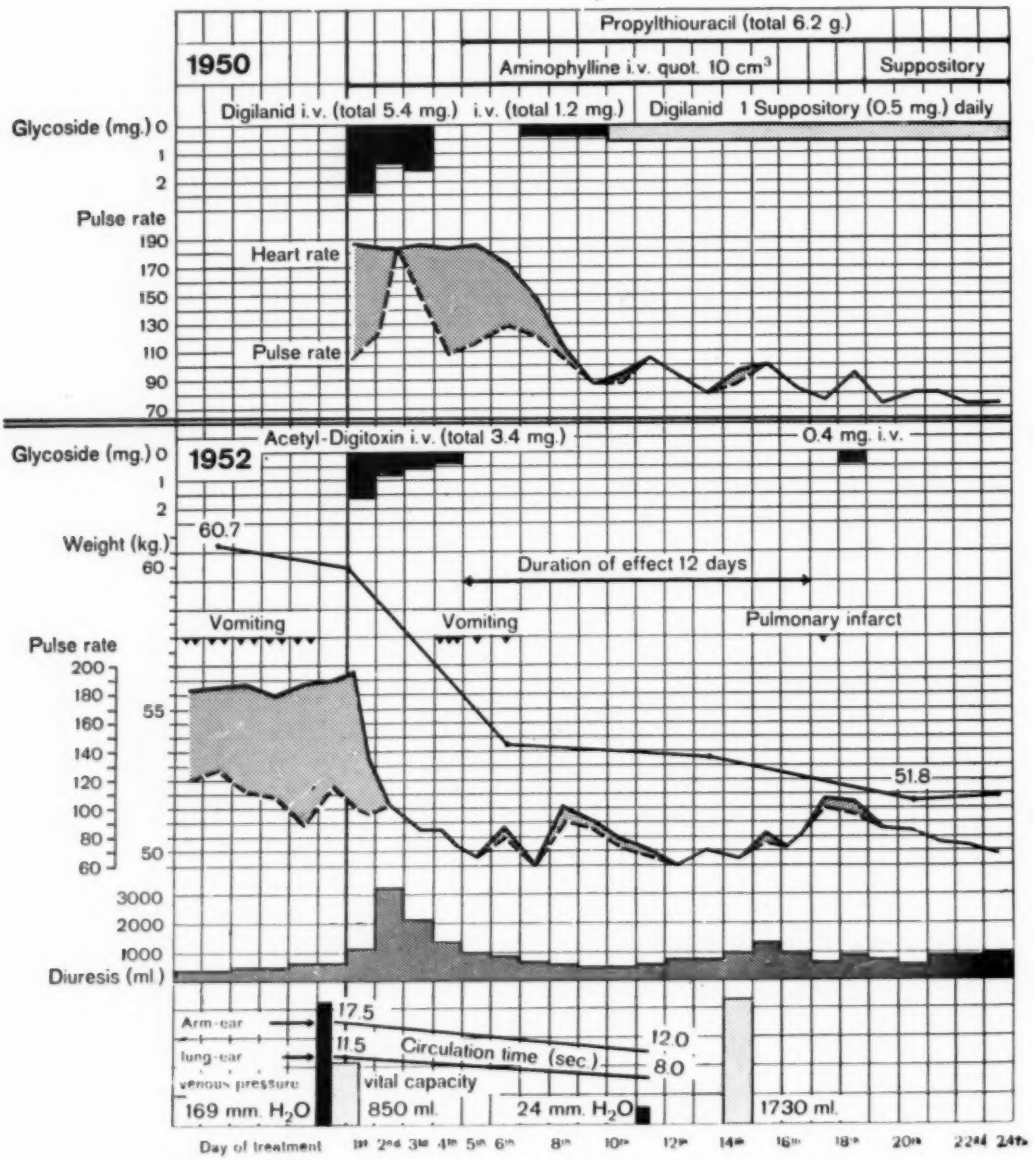

Fig. 3.—Comparison between different glycosides: Acetyl-digitoxin reduces the heart rate more than Digilanid, given intravenously, in the same patient, a 56-year-old woman with hyperthyroidism, myocardial degeneration, and auricular fibrillation with high ventricular rate.

1950: Basal metabolic rate +16 per cent. During treatment with Digilanid the pulse rate was gradually reduced only when propylthiouracil was also given.

1952: Basal metabolic rate +24 per cent. Large intravenous doses of acetyl-digitoxin alone promptly reduced heart rate to normal, exerted a good diuretic effect, reduced weight by 8 kg., decreased venous pressure and circulation time, and increased vital capacity. Digitalization within 24 hours by 2.0 mg. given intravenously. Minimum toxic dose 3.4 mg. Duration of effect 12 days.

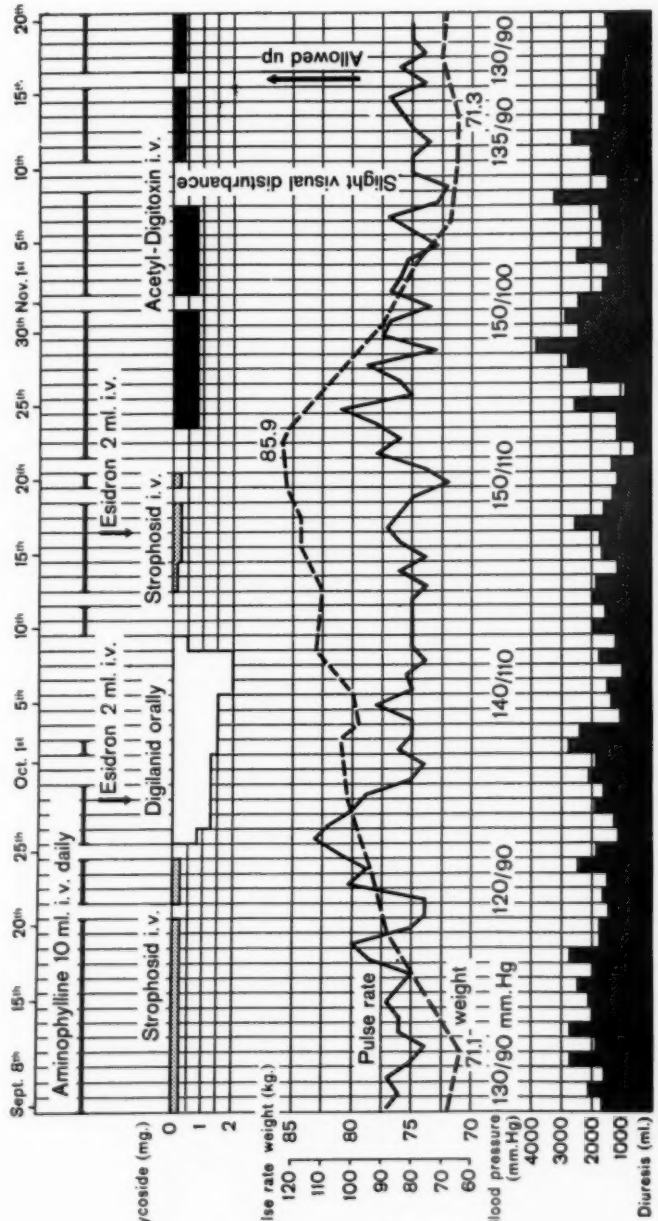

Fig. 4.—Comparison between different glycosides: The diuretic effect of acetyl-digitoxin, given intravenously, proved superior to that of Strophosid and Digilanid in a 55-year-old man with myocardial degeneration, heart failure, sinus tachycardia, septic pulmonary infarct, and bronchial asthma. Despite daily intravenous injections of ¼ mg. Strophosid, large doses of Digilanid given by mouth, and two injections of a mercurial diuretic, cardiac failure became more severe. Intravenous administration of acetyl-digitoxin, initially 0.8 mg. daily, and subsequently 0.4 mg. daily, produced marked diuresis (exceeding intake), loss of weight of 14 kg., and improvement in general condition.

maintenance dose being 0.2 mg. (0.1 to 0.4 mg.) intravenously, or 0.3 mg. (0.1 to 0.6 mg.) by mouth. The latter dose usually has to be increased somewhat when the patient resumes work. The largest doses are required in cases of myocardial degeneration, hypertensive heart failure and, as was to be expected, in patients with hyperthyroidism.

Comparison with other glycosides: Sixteen patients, whose response to acetyl-digitoxin was unsatisfactory, were subsequently treated with Strophosid, ouabain, or Cedilanid. In this series acetyl-digitoxin proved superior to Strophosid in three instances, while ouabain and Strophosid had a somewhat more powerful effect than acetyl-digitoxin in two cases each. In conclusion, two examples (Figs. 3 and 4) may be given to illustrate that, if other glycosides fail, acetyl-digitoxin may either have a better diuretic effect or reduce the heart rate to a greater degree, and thereby restore compensation in patients in whom such a fortunate outcome seems beyond hope. With the introduction of acetyl-digitoxin a very effective glycoside has been added to the preparations used in the treatment of heart disease.

SUMMARY

1. Acetyl-digitoxin is a glycoside obtained from *Digitalis lanata* which is well absorbed from the alimentary tract, acts relatively quickly, greatly reduces the heart rate, and has a pronounced diuretic effect. It is well tolerated and has a wide therapeutic margin. Because of these properties this glycoside, given orally or parenterally, has proved valuable especially in cases of cardiac failure with tachycardia, such as auricular fibrillation with high ventricular rate, auricular flutter, and paroxysmal tachycardia. Because of its high rate of fixation, more persistent action, and cumulation, it is well suited for the maintenance treatment of patients with chronic cardiac failure. As its effect is more quickly reversible than that of digitoxin, treatment with acetyl-digitoxin can be more easily controlled.

2. Signs of intoxication occurring as a result of overdosage disappear within 1 to 3 days of discontinuing treatment. They correspond to those produced by other digitalis glycosides. Signs of local irritation due to the alcohol content of the solution occurring on intravenous injection can be avoided by diluting one part of the ampule solution with three parts of glucose or aminophylline.

REFERENCES

1. Augsberger, A.: Personal communication.
2. Batterman, R. C., and DeGraff, A. C.: Comparative Study on the Use of the Purified Digitalis Glycosides, Digoxin, Digitoxin and Lanatoside C, for the Management of Ambulatory Patients With Congestive Heart Failure, Am. Heart J. **34**:663, 1947.
3. Callebaut, C., Lequime, J., and Denolin, H.: Détermination oxymétrique de la vitesse circulatoire chez l'homme, Acta cardiol. (Brux.) **5**:137, 1950.
4. DeGraff, A. C.: Clinical Comparison of the Cardiac Glycosides, New York J. Med. **45**:1803, 1946.
5. DeGraff, A. C., and Batterman, R. C.: Recent Advances in Digitalis Therapy With Particular Attention to the Use of Pure Glycoside, M. Clin. North America **26**:929, 1942.
6. DeGraff, A. C., Batterman, R. C., and Rose, O. A.: Digitoxin, Its Evaluation for Initial Digitalization of the Patient With Congestive Heart Failure, J.A.M.A. **138**:475, 1948.

7. Diefenbach, W. D., and Meneely, J. K.: Digitoxin—A Critical Review, Yale J. Biol. & Med. **21**:421, 1949.
8. Forster, G., and Lottenbach, K.: Oxymetrische Bestimmung der Kreislaufzeit, Cardiologia **23**:181, 1953.
9. Gernandt, B., and Nylin, G.: The Relation Between Circulation Time and the Amount of the Residual Blood of the Heart, Am. Heart J. **32**:411, 1946.
10. Gold, H., Kwit, N. T., Cattell, M., and Travell, J.: Studies on Purified Digitalis Glycosides: IV. The Single Dose Method of Digitalization, J.A.M.A. **119**:928, 1942.
11. Kjelberg, S. R., Lönroth, H., and Rudhe, U.: The Effect of Various Factors on the Roentgenological Determination of the Cardiac Volume, Acta Radiol. **35**:413, 1951.
12. Knutson, R. B., Taylor, B. E., Ellis, E. J., and Wood, E. H.: Symposium on in Vivo Photometry of Blood in Human Beings; Studies on Circulation Time With the Aid of Oximeter, Proc. Staff Meet., Mayo Clin. **25**:405, 1950.
13. Lindgren, I.: Continuous Measurement of Arterial Oxygen Saturation in Man, Cardiologia **13**:226, 1948.
14. Löffler, W., Essellier, A. F., and Forster, G.: Acetyl-digitoxin, ein neues herzwirksames Glykosid. Klinisch-pharmakologische Untersuchungen, Schweiz. med. Wchnschr. **83**:290, 1953.
15. Matthes, K.: Kreislaufuntersuchungen am Menschen mit fortlaufend registrierenden Methoden, Stuttgart, 1951, Georg Thieme.
16. Moritz, F., and v. Tabora, D.: Ueber eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, Deutsches Arch. f. klin. Med. **98**:475, 1910.
17. Nativelle, C. A.: Sur la Digitaline cristallisée, J. de Pharmacie **9**:255, 1869.
18. Oettel, H. J.: Chemie, Pharmakologie und Klinik der Herzglykoside, Ergebn. inn. Med. **63**:418, 1943.
19. Rothlin, E., Bircher, R., and Schalch, W. R.: Zur Pharmakologie des Acetyl-digitoxin-α, Schweiz. med. Wchnschr. **83**:267, 1953.
20. Stoll, A., and Kreis, W.: (a) Acetyldigitoxin-α und Acetyldigitoxin-β. 30. Mittlg. über Herzglykoside, Helv. chim. Acta **35**:1318, 1952.
(b) Acetyl-digitoxin, Schweiz. med. Wchnschr. **83**:266, 1953.
21. Wexler, J., and Whittenberger, J. L.: An Objective Method for Determining Circulation Time From Pulmonary to Systemic Capillaries by the Use of the Oximeter, J. Clin. Investigation **25**:447, 1946.

THE CEREBRAL HEMODYNAMIC RESPONSE TO THE XANTHINE COMPOUND, PAREPHYLLIN (DIETHYL-AMINOETHYL THEOPHYLLINE HYDROCHLORIDE)

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AMINOPHYLLINE has been observed to decrease cerebral blood flow in normotensive control subjects,[1] patients with heart failure,[2] and patients with hypertension associated with severe headache.[3] At least in the latter group of patients, the cerebrospinal fluid pressure decreases concurrently with the reduction in cerebral blood flow. Recently a xanthine compound (Parephyllin) (Soluphylline or R-3588)* has been introduced which has gained widespread use in France[4,5] under the trade name Soluphylline. It produces less gastric irritation than aminophylline and, therefore, it can be given in large doses orally. In addition, it is not irritating by the intramuscular route of administration. Because of these qualities, it seemed worthwhile to study the pharmacodynamics of this drug and to compare it with aminophylline. The current study is concerned with an evaluation of the cerebrovascular hemodynamic response to this compound (Parephyllin).

METHODS

One normotensive subject and six hypertensive patients, three of whom were in heart failure, were studied. This was a sample group which was similar to patients on whom similar observations had previously been made with aminophylline.[2,3] The ages ranged from 32 to 57 years. The hemoglobin was in excess of 11 grams in all of the patients studied. The studies were done with the patients in the supine position. Measurements of pulse rate and respiratory rate were made during the control period and repeatedly after the drug was administered. The cerebral blood flow was determined by the nitrous oxide technique[6] in the manner previously described.[2,3] After suitable control periods, 0.5 Gm. of the drug was administered by the intravenous route in 100 c.c. of saline over a 20-minute period. After an additional 5-minute delay period, observations on cerebral blood flow were again repeated. Cerebral oxygen

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consumption was determined as previously described.[6] Mean arterial blood pressure was determined by direct intra-arterial manometry. The effect of the drug on the cerebrospinal fluid pressure was determined by an ordinary spinal fluid pressure manometer. After observations were made in the relaxed position, both before and after the drug was administered, the patient was made to raise the abdominal pressure by straining (CAP and DAP, Table I). Observations on the cerebrospinal fluid pressure were recorded during the control period and 30 minutes after administering the drug.

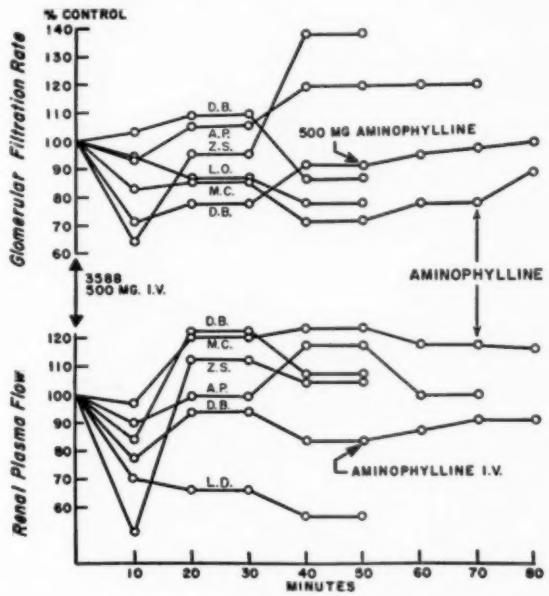

Fig. 1.—Renal hemodynamic response to the intravenous administration of 0.5 Gm. of Parephyllin. (Courtesy Am. J. M. Sc.[8])

RESULTS

The observations on cerebral hemodynamics are recorded in Table I. By contrast to aminophylline, Parephyllin (R-3588) appeared to have very little effect on cerebral blood flow or on cerebrospinal fluid pressure. There were two exceptions and in both of these the cerebrospinal fluid pressure decreased as the cerebral blood flow was reduced. Despite the absence of altered cerebral hemodynamics, dizziness and anxiety were quite commonly observed. There was also a tendency for oxygen consumption to increase, suggesting that the drug increases cerebral metabolism. Hypertensive headaches were observed in two patients, only one of whom showed a decrease in cerebral blood flow with subsequent improvement in her headache.

There was very little alteration in cerebral blood (arterial and venous) oxygen and carbon dioxide. The arterial oxygen content usually increased somewhat, apparently a reflection of increased aeration in the lungs. Despite the absence of reduced cerebral blood flow, there was a slight increase in arteriovenous oxygen difference and in oxygen uptake by the brain.

TABLE I. CEREBRAL HEMODYNAMIC RESPONSE TO PAREPHYLLIN (R-3588)

PATIENT	PULSE RATE		MEAN BLOOD PRESSURE		CEREBRAL‡ BLOOD FLOW		CVR†		CEREBRAL O_2 UPTAKE°		HEMATOCRIT		CEREBROSPINAL*** FLUID PRESSURE				JUGULAR§ PRESSURE		SIDE REACTIONS
	C	D	C	D	C	D	C	D	C	D	C	D	C	CAP	D	DAP	C	D	
1.**	88	90	146	143	41	34	3.6	4.2	2.5	2.7	47	47	300	450	170	280	8.1	7.5	Dizzy, anxiety
2.	84	100	88	76	37	35	2.4	2.2	2.3	2.8	32	30	200	350	210	320	11.5	6.8	None
3.*	92	92	127	120	30	28	4.2	4.3	2.6	2.7	46	46	180	280	130	200	12.2	10.0	Dizzy, nausea
4.*	92	94	160	150	45	51	3.6	2.9	2.4	4.5	37	36	190	300	180	250	10.2	9.8	None
5.*	92	92	144	150	49	47	2.9	3.2	3.1	3.9	42	42	300	500	380	500	21.0	12.8	Anxiety
6.	104	90	153	136	58	44	2.6	3.1	2.8	3.2	46	48	390	500	330	450	—	—	None
7.	72	64	123	130	55	60	2.2	2.2	2.4	2.8	43	44	80	210	180	360	—	—	Dizzy, anxiety
Mean	89	89	134	129	45	43	3.1	3.2	2.6	3.2	42	42	234	370	226	337	12.6	9.4	
Mean (%) of Control		100		96		96		103		123		100						75	

* Associated heart failure
** Headache relieved following injection
*** Cerebrospinal fluid pressure in mm. water
CAP Control cerebrospinal fluid pressure following increased abdominal pressure
DAP Cerebrospinal fluid pressure following drug with increased abdominal pressure
C Control
D Following drug (Parephyllin 0.5 Gm. I.V.)
MBP Mean blood pressure mm. Hg: direct arterial manometry
° Cerebral oxygen uptake ml./100 gram brain/minute

† Cerebral vascular resistance— $\frac{\text{Mean blood pressure}}{\text{Cerebral blood flow}}$

‡ Cerebral blood flow—ml./100 gram brain/minute.
§ Jugular pressure—cm. of water.

TABLE II. EFFECT OF PAREPHYLLIN (R-3588) ON CEREBRAL BLOOD OXYGEN AND CARBON DIOXIDE

PATIENT	RESPIRATION RATE		ARTERIAL O_2 VOLUME (%)		VENOUS O_2 VOLUME (%)		ARTERIOVENOUS O_2 VOLUME (%)		ARTERIAL CO_2 VOLUME (%)		VENOUS CO_2 VOLUME (%)		ARTERIAL P CO_2* MM./HG	
	C	D	C	D	C	D	C	D	C	D	C	D	C	D
1.	21	22	15.5	16.2	9.3	8.4	6.2	7.8	53.4	52.0	59.6	59.8	40	32
2.	16	18	12.4	13.9	6.2	5.8	6.2	8.1	49.2	47.4	54.9	55.1	41	39
3.	21	24	15.2	16.3	6.4	6.6	8.8	9.7	36.0	34.5	44.9	44.2	33	32
4.	12	12	13.7	15.9	8.3	7.1	5.4	8.8	42.8	41.3	47.4	50.6	38	40
5.	14	15	12.0	14.0	5.7	5.7	6.3	8.3	42.7	41.8	49.6	49.6	42	42
6.	16	20	18.0	18.5	13.1	11.2	4.9	7.3	41.6	40.0	47.2	48.2	39	35
7.	18	16	17.5	18.1	13.1	13.4	4.4	4.7	37.2	37.0	33.1	34.0	41	44
Mean	17	18	14.9	16.1	8.9	8.3	6.0	7.8	43.3	42.0	48.1	48.8	39	38
Mean (%) of Control		106		108		93		130		97		101		97

*Arterial partial pressure of carbon dioxide in mm. Hg

TABLE III. RESPONSE OF PAREPHYLLIN AS COMPARED TO AMINOPHYLLINE IN VARIOUS TYPES OF PATIENTS STUDIED*

DRUG	NO. OF PATIENTS STUDIED	TYPE OF PATIENTS	CEREBRAL BLOOD FLOW ML./100 GRAM			CEREBROVASCULAR RESISTANCE†			CEREBRAL O_2 UPTAKE ML./100 GRAM/MIN.			MEAN BLOOD PRESSURE MM. HG			CEREBROSPINAL FLUID PRESSURE MM. WATER		
			C	D	% CONT.	C	D	% CONT.	C	D	% CONT.	C	D	% CONT.	C	D	% CONT.
Parephyllin	7	Hypertension	45	43	96	3.1	3.2	103	2.6	3.2	123	134	129	96	234	226	97
Aminophylline[1]	10	Normal	59	44	75	1.7	2.1	124	3.8	3.8	100	93	91	98	—	—	—
Aminophylline[2]	17	Heart failure	45	30	67	2.6	3.8	146	3.2	2.6	81	114	108	95	—	—	—
Aminophylline[3]	9	Hypertension with headaches	53	36	68	3.0	4.3	143	3.6	3.3	92	151	141	93	210	132	63
Caffeine[3]	7	Hypertension with headaches	54	47	87	2.7	3.3	122	3.2	3.5	109	146	152	104	172	141	82

*Mean values for entire groups of patients studied
C—Control observations
D—Observations after drug
% Cont.—Per cent of control (mean values); control = 100 per cent
† $\frac{\text{Mean blood pressure}}{\text{Cerebral blood flow}}$

DISCUSSION

The cerebral hemodynamic response to Parephyllin is not equivalent to the response to aminophylline in the normal subject or in the hypertensive and cardiac patient. Whereas, aminophylline consistently reduces cerebral blood flow and cerebrospinal fluid pressure, this is only an occasional response to Parephyllin. The jugular pressure was usually reduced following the administration of Parephyllin, which response is also observed after the administration of aminophylline and may be due to a direct cardiac stimulant effect of the drug. Previous observations[7] have also indicated that the renal hemodynamic response is different from that of aminophylline. The glomerular filtration rate and renal plasma flow are both temporarily depressed after Parephyllin (Fig. 1), whereas aminophylline either does not alter these functions or it tends to increase them. Parephyllin[8] likewise exerts only a weak diuretic effect indicating that the drug is of little value as a diuretic either alone or in combination with mercurials.[8]

It is interesting that Parephyllin arrests Cheyne-Stokes respiration much as aminophylline does. This suggests a direct stimulant effect on the respiratory center. We had previously entertained the idea[2] that the reduction in cerebral blood flow and subsequent anoxia of the respiratory center following the administration of aminophylline might be responsible for the ability of this drug to arrest Cheyne-Stokes respiration. However, the fact that such a closely related compound as Parephyllin produces the same response without reducing cerebral blood flow suggests that the therapeutic response to these compounds is probably a direct stimulant effect of the drugs rather than an effect resulting from altered hemodynamics. Since Parephyllin can be administered by the intramuscular route it may be a useful agent for the treatment of patients with Cheyne-Stokes respiration. Again because of the ease of both intramuscular and oral routes of administration this agent should be investigated for its effect on the heart and bronchial tree. The fact that the arterial oxygen increased in nearly all patients suggests that it may be an effective bronchodilator.

SUMMARY AND CONCLUSIONS

Observations have been made on the cerebral hemodynamic response to Parephyllin, a soluble salt of theophylline which can be given in large doses orally and intramuscularly without causing local reactions. In contrast to aminophylline, Parephyllin does not reduce cerebral blood flow. Since this agent may relieve Cheyne-Stokes respiration much as aminophylline does, it seems quite likely that the mode of action for both drugs is by their direct stimulant effect on the respiratory center.

REFERENCES

1. Wechsler, R., Kleiss, L., and Ketty, S.: The Effects of Intravenously Administered Aminophylline on Cerebral Circulation and Metabolism in Man, J. Clin. Investigation **29**:28, 1950.
2. Moyer, J. H., Miller, S. I., Tashnek, A., and Bowman, R.: The Effect of Theophylline With Ethylene Diamine (Aminophylline) on Cerebral Hemodynamics in the Presence of Cardiac Failure With and Without Cheyne-Stokes Respiration, J. Clin. Investigation **31**:267, 1952.

3. Moyer, J. H., Tashnek, A., Snyder, H., and Bowman, R.: The Effect of Theophylline With Ethylene Diamine (Aminophylline) on Cerebral Hemodynamics and Cerebrospinal Fluid Pressure in Patients With Hypertensive Headaches, Am. J. M. Sc. **224**:377, 1952.
4. Cronheim, Georg: Personal communication.
5. Riker Laboratories, Inc., Department of Clinical Research: Personal communication.
6. Kety, S. S., and Schmidt, C. F.: The Nitrous Oxide Methods for the Quantitative Determination of Cerebral Blood Flow in Man: Theory, Procedure, and Normal Values, J. Clin. Investigation **27**:476, 1948.
7. Livesay, W. R., and Moyer, J. H.: The Renal Hemodynamic Effects of a Xanthine Compound, Diethyl Aminoethyl Theophylline Hydrochloride (Parephyllin), J. Pharmacol. & Exper. Therap. **109**:123, 1953.
8. Silvertho:ne, M., and Moyer, J. H.: Observations on the Diuretic Response to Parephyllin (R-3588), Neohydrin, and Mercuhydrin When Administered Alone and in Combination, Am. J. M. Sc. **227**:83, 1954.

Clinical Reports

VENTRICULAR TACHYCARDIA DUE TO IDIOPATHIC PERICARDITIS CONTROLLED BY SIMULTANEOUS INTRAVENOUS PROCAINE AMIDE AND QUINIDINE

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THIS case is reported because to our knowledge ventricular tachycardia due to idiopathic pericarditis has not been described. Furthermore, we were unable to find a prior report on the simultaneous intravenous use of procaine amide and quinidine. We used these drugs simultaneously because we were unable to convert the arrhythmia by administering increasingly large doses of each of them alone.

Ventricular tachycardia, if uncontrolled, may lead to a fatal termination from ventricular fibrillation, cardiac arrest, or cardiac decompensation. It is an arrhythmia of independent ventricular origin, usually occurring simultaneously with a slower sinoauricular rhythm, although any auricular rhythm may be present. The physiologic and pathologic mechanism of this arrhythmia has never been definitely established. It has been postulated that the stimuli arise either in a circular movement in a ring of ventricular tissue, or in a single ectopic focus in the ventricular myocardium.[1-3] It is sometimes impossible to distinguish this arrhythmia from a supraventricular tachycardia with aberrant ventricular conduction, but the electrocardiographic demonstration of an independent atrial rhythm or of transitional complexes between those of ventricular and supraventricular origin is helpful.[4]

Procaine amide is similar to procaine, differing solely by the substitution of an amide group for the ester group present in procaine. Its pharmacologic action is not thoroughly understood. It has been described as having a quinidine-like action.[5,6] It has a similar but more enduring action than procaine.[7] In the turtle heart it raises the threshold for electrical stimulation and thus lengthens the ventricular conduction time. Unlike quinidine it does not depress contractility, nor does it affect rhythmicity or the refractory period.[5] It depresses auricular excitability.[5,8] It usually depresses ventricular excitability but has been observed in animal and human hearts to be followed by ventricular fibrillation,[9] ventricular tachycardia,[10,11] premature ventricular systoles,[12] complete

From the Medical Service, United States Army Hospital, Camp Gordon, Ga.
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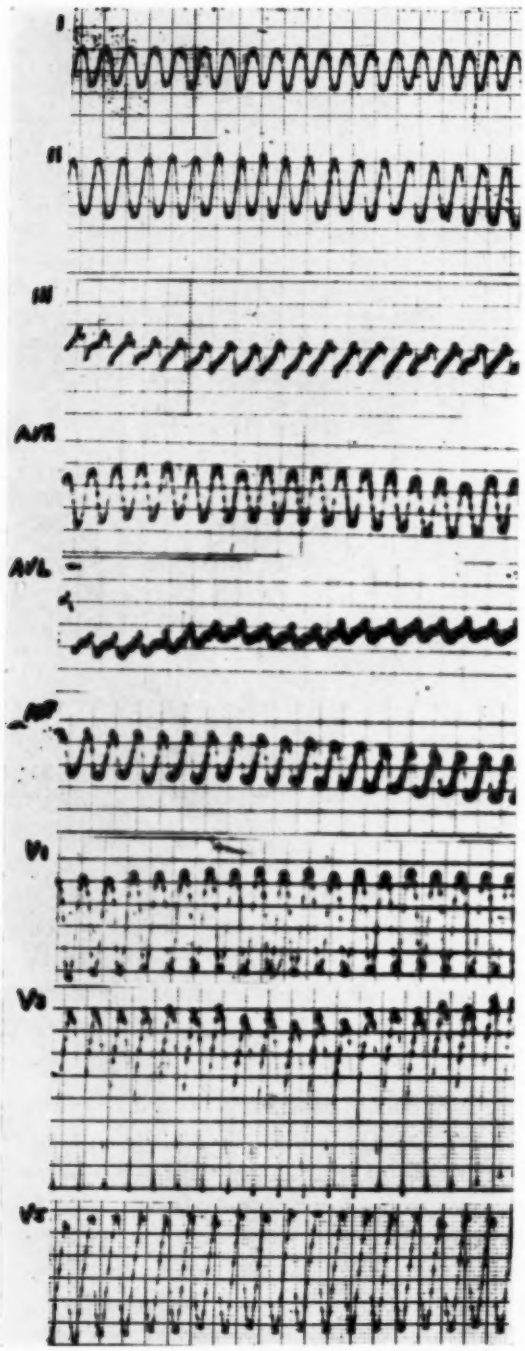

Fig. 1.—Electrocardiogram taken on admission demonstrating ventricular tachycardia.

block, bundle branch block, and depression of the idioventricular pacemaker.[5] Dutta[6] has demonstrated a blocking action in the superior cervical ganglion, much like atropine and quinidine. Toxicity is relatively mild, but hypotension may be marked with intravenous use. Mild gastrointestinal symptoms are common; and rash, fever, urticaria, and agranulocytosis have been observed.[12-15] Its potency has been calculated by Schaffer as approximately one-fourth that of quinidine.[8,16]

The action of quinidine on the heart is well known and may be summarized as increasing the refractory period, decreasing myocardial excitability, and slowing conduction.[17] Clagett[18] has reviewed the literature on intravenous quinidine and reported a patient who was given a maximum single intravenous dose of quinidine sulfate of 3.25 Gm. with successful conversion of ventricular tachycardia to sinus rhythm.

CASE REPORT

This patient was a 21-year-old white male soldier, admitted to the U. S. Army Hospital at Camp Gordon, Georgia, on Feb. 18, 1953. He was in apparent good health until the afternoon of admission. At this time while sitting at a desk he experienced a sudden onset of rapid heart action, faintness, sweating, substernal pain, and vomiting, persisting for one hour until the time of admission. He stated that he had had three or four mild and brief attacks of palpitation in the last five years but offered no other history of any medical problem, including rheumatic fever and its equivalents, heart disease, tuberculosis, or recent respiratory infection.

Physical examination revealed a pale, apprehensive, sweating male. The blood pressure was unobtainable. Auscultation revealed a heart rate of 280 per minute, and a coarse precordial murmur which we were unable to time. Electrocardiogram showed a ventricular tachycardia (Fig. 1). Blood count showed 18,600 leukocytes with 81 per cent neutrophils. Sedimentation rate on admission was 18 mm. in one hour by the Wintrobe method and rose to 29 mm. on the twelfth hospital day. Urinalysis and serologic tests for syphilis were normal. The antistreptolysin titer on the tenth day was reported as 625 units.

On admission the patient was given 0.2 Gm. of quinidine sulfate by mouth, but he vomited thirty minutes thereafter. During the following six hours he was given 1.0 Gm. of procaine amide intravenously, 1.0 Gm. of calcium gluconate intravenously, and 16 mg. of morphine sulfate subcutaneously without conversion to sinus rhythm. The tachycardia persisted over the following two days, despite the administration of 1.2 Gm. of quinidine lactate intramuscularly in divided doses over a six-hour period, 2.0 Gm. of procaine amide given intravenously over twenty minutes, 2.0 Gm. magnesium sulfate injected intravenously, and 3.2 Gm. of quinidine gluconate administered intravenously over four hours. At this time the patient had a fever of 101° F. Roentgenogram of the chest showed the heart to be at the upper limits of normal, and the hilar vascular markings to be increased. The arm-to-tongue circulation time with Decholin Sodium given in the right median cubital vein was twenty-five seconds. On the morning of the third hospital day the patient was given 50 mg. of quinidine gluconate and 50 mg. of procaine amide alternately, intravenously, at one-minute intervals. After a total dose of 1.5 Gm. of each drug during a period of sixty minutes, the patient reverted to sinus rhythm (Fig. 2). He had frequent singultus and vomiting during this time, but no other untoward effects. After conversion, auscultation revealed a pericardial friction rub which persisted for the following ten days. He ran a low grade fever up to 101° F. for the subsequent week, and thereafter was afebrile. He was given oral quinidine sulfate 0.3 Gm. every six hours for seven days, and then no further medication. He was followed up until the present time and continued in normal sinus rhythm.

The tracing taken immediately after conversion showed no P waves. The S-T segments and T waves were abnormal (Fig. 2). At no time was there electrocardiographic evidence of pericarditis (Fig. 3).

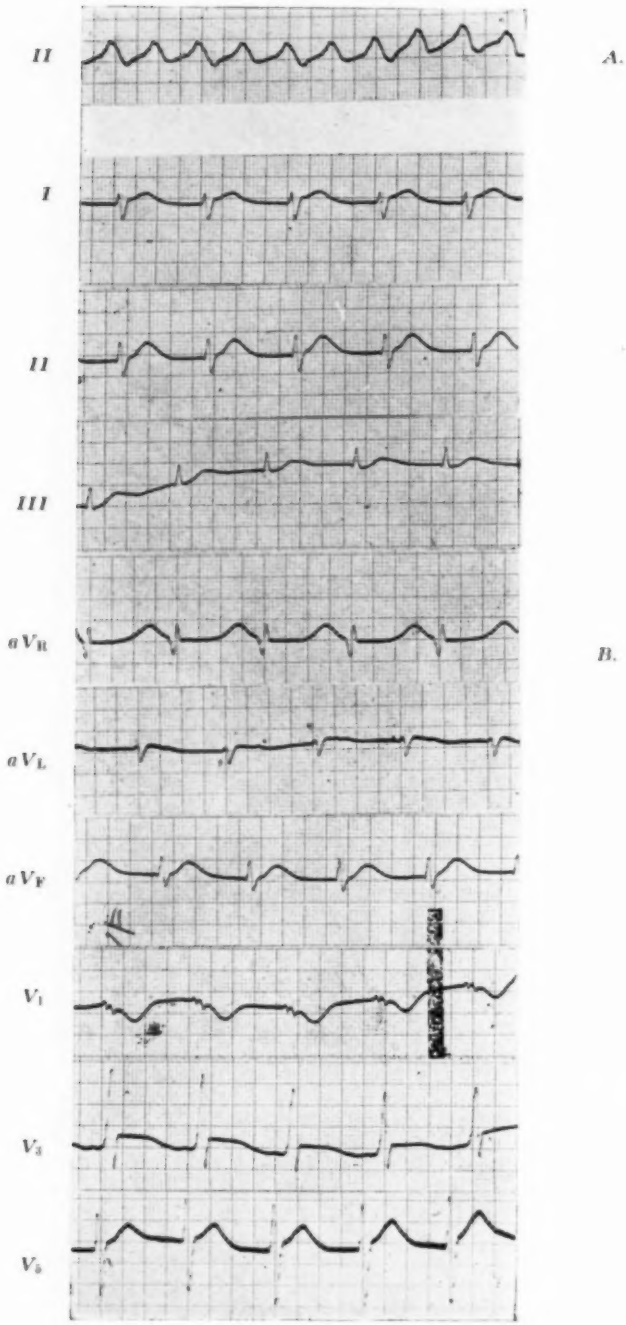

Fig. 2.—*A*, Lead II showing marked slowing of ventricular tachycardia just prior to conversion to sinus rhythm. *B*, Tracing taken just after conversion to sinus rhythm.

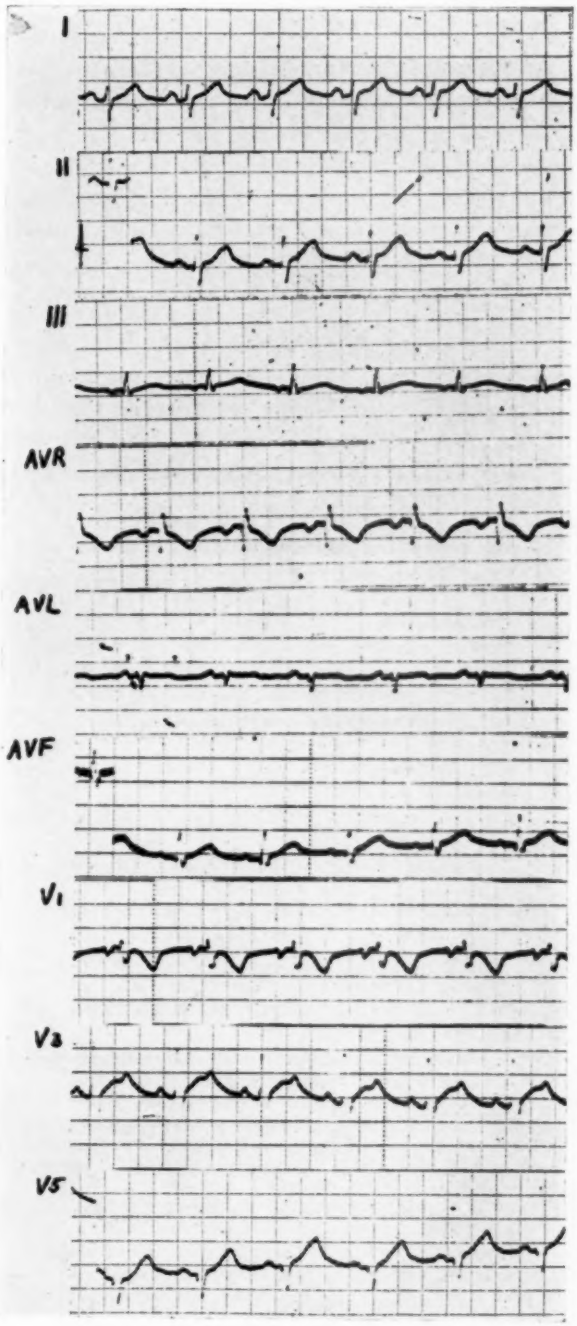

Fig. 3.—Electrocardiogram taken three days after conversion to sinus rhythm.

DISCUSSION

We believe our patient had an idiopathic pericarditis as described in the literature.[19-21] The elevated antistreptolysin titer indicates a streptococcal infection, but the absence of other findings makes rheumatic fever an unlikely diagnosis. The absence of electrocardiographic changes in acute pericarditis has been previously reported.[22] We may postulate that an area of inflamed subepicardial myocardium was the focus producing the ventricular tachycardia.

SUMMARY

A case of ventricular tachycardia is presented. The etiology is believed to be acute idiopathic pericarditis. This arrhythmia could not be controlled by the intravenous administration of 2 Gm. of procaine amide and 3.2 Gm. of quinidine gluconate given on separate occasions. The simultaneous administration of these drugs in a dose of 1.5 Gm. of each caused conversion to sinus rhythm.

ADDENDUM

The patient was last seen May 20, 1953. He complained of dyspnea and precordial discomfort on exertion. Examination showed nothing except a tachycardia of 100 upon standing. A double Master's Test showed the rate to remain fairly fast during the period of recovery. There was no significant change in the P-Q-R-S-T complex. Hence, the patient was sent to limited duty. There has been no clinical or electrocardiographic evidence of recurrence of arrhythmia, despite the fact that he is under no treatment.

REFERENCES

1. Scherf, D., and Boyd, L. J.: Cardiovascular Diseases, Philadelphia, 1947, J. B. Lippincott Company, p. 372.
2. Friedberg, C. K.: Diseases of the Heart, Philadelphia, 1949, W. B. Saunders Company, p. 282.
3. Prinzmetal, M.: Editorial: The Wolf-Parkinson-White Syndrome and Related Phenomena, Am. J. Med. **13**:121, 1952.
4. Dressler, W., and Roesler, H.: The Occurrence in Paroxysmal Ventricular Tachycardia of Ventricular Complexes Transitional in Shape to Sinoauricular Beats. A Diagnostic Aid, Am. Heart J. **44**:485, 1952.
5. Wedd, A. M., Blair, H. A., and Warner, R. S.: The Action of Procaine Amide on the Heart, Am. Heart J. **42**:399, 1951.
6. Dutta, N. K.: Some Pharmacological Properties Common to Atropine, Pethidine, Procaine, and Quinidine, Brit. J. Pharmacol. **4**:197, 1949.
7. Mark, L. C., Berlin, I., Kayden, H. J., Rovenstine, H. A., Steele, J. M., and Brodie, B. B.: The Action of Procaine Amide (N 1-(2-diethylaminoethyl) p-amino-benzamid) on Ventricular Arrhythmias, J. Pharmacol. & Exper. Therap. **98**:21, 1950.
8. Schaffer, A. J., Blumenfeld, S., Pitman, E. R., and Dix, J. H.: Procaine Amide: Its Effect on Auricular Arrhythmias, Am. Heart J. **42**:115, 1951.
9. Read, J. M.: Fatal Ventricular Fibrillation Following Procaine Amide Therapy, J.A.M.A. **149**:1390, 1952.
10. Wetherbee, D. G., Holzman, D., and Brown, M. G.: Ventricular Tachycardia Following the Administration of Quinidine, Am. Heart J. **43**:89, 1952.
11. Schreiner, G. E., and Kelly, R. T.: Ventricular Tachycardia Following Procaine Amide Hydrochloride (Pronestyl) and Quinidine, Am. Heart J. **43**:749, 1952.
12. Bakos, A. C. P., and Askey, J. M.: Fever Due to Procaine Amide Hydrochloride Therapy, J. A. M. A. **149**:1393, 1952.
13. Hellman, E.: Allergy to Procaine Amide, J. A. M. A. **149**:1393, 1952.
14. Berry, K., Garlett, L., Bellet, S., and Gefter, W. I.: Use of Pronestyl in the Treatment of Ectopic Rhythms, Treatment of Ninety-eight Episodes in Seventy-eight Patients, Am. J. Med. **11**:431, 1951.

15. Miyoko, I., Millar, J., and Townsend, J. H.: Agranulocytosis Following Maintenance Dosage of Pronestyl; Report of a Severe Case With Recovery, J. A. M. A. **147**:652, 1951.
16. Schaffer, A. I.: Procaine Amide Compared With Quinidine as a Therapy for Arrhythmias, Am. Heart J. **42**:597, 1951.
17. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, 1941, Macmillan Company, p. 539.
18. Clagett, A. H., Jr.: Intravenous Use of Quinidine With Particular Reference to Ventricular Tachycardia, Am. J. M. Sc. **220**:381, 1950.
19. Levy, R. L., and Patterson, M. C.: Acute Serofibrinous Pericarditis of Undetermined Etiology; Study of 27 Cases, Am. J. Med. **8**:34, 1950.
20. Feder, I. A., Hoffman, J. B., and Sugar, H.: Acute Primary Pericarditis, Am. J. M. Sc. **220**:144, 1950.
21. Carmichael, D. B., Sprague, H. B., Wyman, S. M., and Bland, E. F.: Acute Nonspecific Pericarditis, Circulation **3**:321, 1951.
22. Bellet, S., and McMillan, T. M.: ECG Patterns in Acute Pericarditis, Arch. Int. Med. **61**:381, 1938.

PROLONGED SURVIVAL FOLLOWING PERFORATION OF THE INTERVENTRICULAR SEPTUM AS A RESULT OF A MYOCARDIAL INFARCTION

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PERFORATION of the interventricular septum secondary to myocardial infarction is not an unusual event and increasing reports in the literature indicate cognizance of this complication. The clinical syndrome presented in a patient with such a catastrophe is rather specific and usually leads to the diagnosis. A victim of myocardial infarction suddenly develops acute failure of the right side of the heart and at the same time a loud blowing systolic murmur makes its appearance over the precordium. The combination of the infarction plus the appearance of the murmur and subsequent acute heart failure is sufficient evidence that septal perforation has occurred. Death usually follows within a short time after the development of this complication. The prediction had been made that some of these individuals might live for a goodly length of time following perforation of the septum. A few cases have been so reported. The following case is reported of a septal perforation which was diagnosed ante mortem and in which the patient survived despite the presence of severe congestive heart failure for many months.

CASE REPORT

H.A.R. entered the Ancker Hospital on Aug. 31, 1948. He was a white man, 75 years of age, who was a sheep herder. At the time of admission to the hospital he complained of shortness of breath and a crushing pain across his chest. He stated that at two o'clock on the day of admission to the hospital he was shearing his sheep when he suddenly developed a very severe shortness of breath and almost simultaneously a crushing sensation over the front of his chest. Because of the shortness of breath he was unable to lie down and he was brought to the hospital immediately. The past history was uneventful and not relevant to the present illness.

Physical examination revealed a well-developed, well-nourished white male in acute respiratory distress. He was very restless and apprehensive. He was bathed in a cold sweat and had a cyanotic appearance. The physical examination at the time of admission to the hospital was otherwise normal with the exception that râles were found in the bases of both lungs. The blood pressure was 125/100 mm. Hg, the pulse 100, no murmurs were heard, no evidence of cardiac enlargement to physical examination and the rate was regular. It was our impression at the moment that the patient had suffered from a coronary thrombosis with myocardial infarction and acute congestive heart failure. The patient was acutely ill until Sept. 2, 1948, when he developed for the first time a loud "rubbing" systolic murmur in the apical area of his heart. This murmur had not been

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present before. There was increasing evidence that the patient was now developing failure of the right side of the heart. On Sept. 3, the murmur was very well heard particularly at the tip of the sternum. No rub could be felt and the patient had now developed auricular fibrillation. The resident suggested the possibility that the appearance of the murmur in conjunction with evident right-sided heart failure might mean that the patient had suffered a perforation of the interventricular septum. This diagnosis was confirmed by the attending staff. His condition again became very grave, and it was thought he would not survive. Over a period of time, however, the patient gradually recovered from the acute phase of his illness but the auricular fibrillation persisted. On Sept. 6, 1948, with the use of quinidine the auricular fibrillation was converted to a normal rhythm. The murmur remained as before, but there was increasing evidence now of pulmonary congestion. The patient received the usual supportive therapy throughout his illness, including oxygen, anticoagulants, quinidine, digitalis, etc. The patient's condition gradually improved and he was finally discharged from the hospital. At the time of his discharge from the hospital on Oct. 29, 1948, the patient had evidence of severe right-sided heart failure. The patient was treated routinely at home and received diuretics as well as supportive treatment for his cardiac condition. He entered St. Joseph's Hospital on May 9, 1952, and expired shortly after his entrance to the hospital.

The electrocardiogram on Sept. 1, 1948, revealed rapid auricular fibrillation and evidence of an acute anterior infarction. A record taken earlier on Sept. 1, 1948, revealed a normal rhythm but evidence also of an acute anterior infarction. Subsequent records revealed nothing unusual other than periods of auricular fibrillation and evidence of serial changes characteristic of anterior infarction. Portable x-ray of the chest on Sept. 22, revealed pulmonary congestion bilaterally. The film was unsatisfactory because of obesity.

The salient features of the autopsy were a heart weighing 565 grams which exhibited an old left ventricular aneurysm. There was a large scar on the anterior and lateral surfaces of the left ventricle in its distal two-thirds. On opening the chambers there was an old area of infarction corresponding to the distal two-thirds of the interventricular septum in its anterior two-thirds portion. The adjacent left ventricular wall was pale in the corresponding area. The wall was replaced by a scar and thinned out to approximately 2 millimeters. There was an old thrombus in the anterior descending branch of the left coronary artery which was cannulized. Within the scar in the interventricular septal defect near the anterior quarter of the ventricular wall there was a perforation. This defect was 1 to 1.5 cm. in diameter. It was at the junction of the distal one-third and the proximal two-thirds of the interventricular septum on its anterior border. The remaining coronary arteries were sclerotic but not appreciably narrowed. The myocardium on the right side was hypertrophied and the chambers were greatly dilated. The liver revealed severe chronic passive congestion.

CONCLUSIONS

A case is recorded of a myocardial infarction in which septal perforation occurred, following which the patient survived for 41 months. His illness was characterized by severe congestive heart failure. During this time the edema was partially controlled by the use of diuretics and the ascites by paracentesis. This case demonstrates that occasionally a patient with a perforation of the interventricular septum as a result of myocardial infarction may survive for many months.

Critique

AN EVALUATION OF THE TERM "CORONARY INSUFFICIENCY"

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THE term "coronary insufficiency" is widely employed nowadays and is, in our opinion, much abused. It may be informative, it seems to us, to inquire into the meaning of the term and its clinical usefulness.

Original Meaning of the Term.—When the term "coronary insufficiency" was introduced originally, it was meant to describe a certain functional state in which the coronary blood flow was not adequate for the needs of the myocardium.[18] This state of inadequacy occurs in a variety of conditions. The blood supply to parts of the heart muscle is insufficient in syphilitic stenosis of the coronary ostia and in arteriosclerotic stenosis of the arteries of the coronary branches. The insufficiency becomes manifest when exertion, a rise of blood pressure, tachycardia, or an increased amount of pressor amines in the blood raise the demands of the heart for oxygen. The same insufficiency may, even in the absence of a stenosis, occasionally be due to reflex narrowing of a coronary artery, i.e., coronary "spasm" (acute hemorrhage), or to the inability of a coronary artery to widen sufficiently when the requirements of the heart muscle for oxygen are suddenly increased. An insufficient amount of oxygen to the heart muscle is also supplied in anemia, especially during physical exertion. In animal experiments, carbon monoxide intoxication and orthostatic hypotension were found to have similar effects.[1]

Anginal pain often appears with a paroxysmal rise of the blood pressure (hypertensive crisis) with or without pheochromocytoma. It may also occur in mitral stenosis, aortic insufficiency, and aortic stenosis. While the mechanism of anginal pain in these conditions is not entirely clear, it seems certain that myocardial ischemia is present. Here again the term coronary insufficiency has been used to describe the underlying functional state.

In all conditions mentioned, histologic examination has revealed necrosis of myocardial cells, particularly those in the subendocardial layers of the myocardium which are known to be most susceptible to a diminution of blood supply because they are exposed to the high intraventricular pressure. Characteristic electrocardiographic changes, usually consisting of depression of the RS-T segments, have been described and have become accepted as diagnostic for this condition.[1]

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From the outset, the term "coronary insufficiency" has not proved entirely satisfactory. In carbon monoxide intoxication, for example, only the oxygen supply is insufficient, not the coronary arteries. It is equally impossible to assume the presence of an "insufficient" coronary artery in chronic anemia or in tachycardia with anatomically normal coronary vessels. Such objections notwithstanding the term has been found useful and has been readily accepted. It may be recalled that when we speak of "aortic insufficiency" we mean aortic *valve* insufficiency, yet the incorrect term is well understood. It, like so many inaccurate terms in medicine, has not been discarded because it has had according to common parlance a certain meaning widely accepted for many years.

Present Confusion in Use of the Term Coronary Insufficiency.—Confusion arose when the term was used to describe a variety of clinical and pathological conditions, not merely to designate a functional state. Nowadays, coronary insufficiency is often considered a clinical diagnosis without any inquiry as to its cause or mechanism in a given patient. Besides, electrocardiograms are frequently reported as showing the "typical pattern of coronary insufficiency." Even pathologists sometimes state that the patient under discussion "suffered from coronary insufficiency." Clinicians report that certain compounds, khellin-preparations for instance, are helpful in coronary insufficiency.

Such loose use of the term can be found in scientific journals almost every week. We may quote a few examples. One reads that ". . . coronary insufficiency was considered a cause (for pain) but against it was the failure of the pain to respond to nitroglycerine."[10] Thus we are led to believe that the presence or absence of coronary insufficiency can be determined by the response to nitroglycerine. In another recent paper, it is stated, that ". . . it is generally accepted that angina, coronary insufficiency, and coronary occlusion are varying degrees of a common condition namely myocardial ischemia."[22] Here, in agreement with the opinion of many, coronary insufficiency is regarded as a condition more severe than angina pectoris but less severe than coronary occlusion. In another journal a physician asks for help with a diagnosis. His patient had suffered from substernal pain for 90 minutes; the electrocardiogram had remained normal for one week and had then shown only a temporary abnormality of the T wave in Lead aV_L. The answer given by the expert reads, "The changes noted above suggest the condition was coronary insufficiency rather than myocardial infarction."[17] Here again "coronary insufficiency" is offered as a diagnosis, and the possibility of a small infarction is discarded too readily.

Other Definitions and Uses of This Term.—Several recent textbooks of cardiology and electrocardiography describe myocardial infarction, even if associated with coronary thrombosis, under the heading "coronary insufficiency." This is logical since coronary occlusion may be considered as an extreme degree of coronary insufficiency. When we diagnose coronary insufficiency in these patients, however, we necessarily add to the confusion as myocardial infarction is a well known clinical syndrome, easily recognized in most instances. Why use a broad, nonspecific term, when a well-defined pathological and clinical condition can be diagnosed? In most instances it will be impossible to differentiate clinically whether the infarction is caused by thrombosis of a coronary artery, or

whether it is due to long-lasting ischemia when physical exertion or a paroxysmal tachycardia complicates coronary stenosis. Necrosis of muscle fibers is common in the last-named conditions.

Gregg speaks of absolute and relative coronary insufficiency, the former occurring in stenosis and closure of the coronary arteries, the latter caused by an increased oxygen demand, e.g., in hypertrophy of the heart. He also distinguishes between primary coronary insufficiency associated with valvular disease and primary coronary insufficiency caused by arteriosclerosis.[8]

Graybiel states that coronary insufficiency describes a pathophysiologic state which may be due to different causes. "Acute" coronary insufficiency may involve a large or small area of the myocardium and may be slight or absolute. The term chronic coronary insufficiency should be used with caution; it refers to a relatively permanent state brought about by irreversible causes. A severe degree of chronic coronary insufficiency is improbable because it would lead to necrosis; however, mild degrees of chronic coronary insufficiency may persist for years. Graybiel also uses the term "potential" coronary insufficiency to indicate a state of lowered coronary reserve.[7]

A chronic coronary insufficiency is often said to be responsible for the electrocardiographic changes in hypertrophied hearts and is supposed to explain the strain pattern seen in the electrocardiogram of these patients. Since this pattern may persist without change for years and is influenced little or none by exercise, the administration of nitrites or ergotamine, the heart remaining strong and hyperactive, without any evidence of failure over many years, we consider this explanation improbable.

According to Levy acute fatal coronary insufficiency is a term which should be employed to describe the sudden death of some patients with coronary disease, in the absence of coronary thrombosis.[11] We believe that in most patients with coronary disease sudden death is actually due to ventricular fibrillation. In patients with coronary sclerosis, in whom an electrocardiogram was obtained fortuitously at the time of death, ventricular fibrillation was observed.[19] At that time myocardial ischemia may or may not be pronounced.

Term Used as a Synonym for Angina Pectoris.—There is a widespread tendency to use the terms coronary insufficiency and angina pectoris as synonyms.

Danielopolu, who employed the term "coronary insufficiency" very early, calls "coronary insufficiency without coronary disease" the occurrence of anginal pain in healthy individuals during overexertion, such as cycling or mountain climbing. When extensive obstruction of the coronary arteries exists without anginal pain, on the other hand, the diagnosis is said to be "coronary disease without coronary insufficiency."[5]

Confusion has also been due to the fact that the term "angina pectoris" is used by many to describe different situations. Most authors speak of angina pectoris when they mean classical angina on effort. But they also use the word "anginal" for the pain in coronary occlusion, pulmonary embolism, paroxysmal tachycardia, etc. For others, angina pectoris is a symptom, which may appear in a variety of conditions in which coronary insufficiency is said to occur, and these include coronary occlusion. We have always preferred the last definition

From this it follows that angina pectoris is never a complete diagnosis. One should state that a patient suffers from angina pectoris due to coronary sclerosis, or that a patient has angina pectoris caused by aortic stenosis or has a severe attack of anginal pain in the early phase of coronary thrombosis, etc.

It should be re-emphasized that angina pectoris describes a symptom, while coronary insufficiency designates a certain abnormal state. A diminished blood supply to the heart may occur without pain; thus not every coronary insufficiency is accompanied by angina pectoris. Every angina pectoris, however, according to the present conception, is caused by a diminished oxygen supply to the heart or parts of it (coronary insufficiency).

Term Used to Indicate Coronary Disease.—This is a common result of loose thinking. Not infrequently one reads that xanthomatosis leads to coronary insufficiency or that penicillin therapy in syphilitic aortitis occasionally causes coronary insufficiency. In the general practice of medicine the diagnosis of coronary insufficiency at the present time is commonly made whenever the diagnosis of angina on effort or of myocardial infarction is not immediately evident. Unfortunately many physicians regard this as satisfactory and sufficient and do not search for the cause of the existent coronary insufficiency.

Term Used to Designate a Clinical Entity.—The use of the term coronary insufficiency as indicating a clinical entity was popularized by Master and his associates. It was declared a useful term, ". . . when restricted to necrosis or infarction of the heart muscle without complete occlusion."[12]

Later, acute coronary insufficiency was defined as a syndrome of severe myocardial ischemia, more prolonged and more severe than that which occurs in "angina pectoris." It was then stated that acute coronary insufficiency is an entity and that it appears as a result of a sudden increase of cardiac work, or a diminution of cardiac blood flow or of interference with oxygenation of the blood. The clinical signs are, as a rule, according to the authors, not as marked as those in acute coronary occlusion. A fall of the blood pressure, an accelerated sedimentation rate and fever, may or may not be present.[15] In the electrocardiogram Q waves are absent, but a depression of the RS-T segments is usually seen. The situation was confused by the statement that differentiation is necessary between "coronary insufficiency without coronary occlusion" and "coronary insufficiency with acute occlusion."[13] The authors do not try to differentiate between myocardial ischemia and myocardial infarction as one would assume they might. Instead they attempt to show that it is possible to differentiate clinically between myocardial infarction caused by coronary occlusion on one hand and infarction occurring without occlusion of a coronary artery on the other.

DISCUSSION

The terms "intermediate coronrary syndrome,"[7] coronary insufficiency and "coronary failure,"[6] have been used to describe a state between simple angina pectoris (whereby angina on effort is meant) and myocardial infarction. In that state the pain is prolonged but does not last very long, the blood pressure remains normal or falls only slightly, the sedimentation rate does not rise or is only

slightly elevated, fever is absent or slight, leukocytosis is absent or borderline. The electrocardiogram shows no Q waves and no elevation of the RS-T segments. This concept certainly requires correction. It has been established that in myocardial infarctions, particularly those caused by the occlusion of a small artery, a fall of blood pressure, fever, changes of the sedimentation rate, or leukocytosis may be slight or absent. The electrocardiogram often shows only changes of the T waves. In most cases in which coronary insufficiency is diagnosed nowadays, because the pain and the clinical picture is "in between" angina on effort and the attack of an infarction of a large area of the myocardium, it is our opinion that a small myocardial infarction exists. Such small infarctions "slight coronary attacks"[16] belong to the coronary syndrome which is most frequently overlooked at the present time. Some of our patients have had hundreds of such attacks over several years, with pain sometimes lasting for hours and with no, or delayed effect of nitroglycerine, with only occasional and slight transient rise of temperature, and a transient occasional flattening or inversion of the T waves in some leads. At post mortem, many scattered areas of myocardial fibrosis are found. The diagnosis of "coronary insufficiency" in such patients without any attempt to arrive at a correct anatomic diagnosis should be rejected. It does not help in the evaluation or management of the patient.

It is frequently asserted that the electrocardiographic finding characteristic of coronary insufficiency is a depression of the RS-T segment. This is incorrect. Depression of the RS-T segments and an inversion of the T waves, to be sure, are common when the subendocardial layers of the myocardium are damaged experimentally.[2] Moreover, in spontaneous attacks of angina on effort as well as in those induced by the exercise test, depression of the RS-T segment is most common. The electrocardiogram in myocardial anoxia may, however, show only simple inversion of the T waves without changes of the RS-T segment. Inversion of the T waves is the only characteristic change seen in many patients following an acute hemorrhage.[20] On the other hand, marked elevation of the RS-T segment, as seen in acute infarction, but disappearing within a few minutes, has been frequently observed following exercise in patients with coronary stenosis.[4,21]

When an attack of anginal pain appears at rest, when it is prolonged, and when the response to nitroglycerine is unsatisfactory or delayed, it is impossible to state whether we are dealing with the premonitory syndrome preceding coronary thrombosis, or whether an infarction or several small infarctions exist. Prolonged observation usually will supply the answer.

Thus, the term coronary insufficiency is no more a diagnosis than the term angina pectoris. There are many conditions which give rise to coronary insufficiency or are accompanied by it. In every instance an attempt should be made to establish an etiologic and if possible, an anatomic diagnosis. The conditions mentioned, namely, simple angina on effort, the premonitory syndrome, small or large infarctions, are not the only ones to be considered. One should bear in mind paroxysmal tachycardia, paroxysmal flutter, and fibrillation with or without electrocardiographic evidence of the posttachycardia syndrome.[3] Furthermore, at the onset of an acute internal hemorrhage it may be impossible to rule out the presence of an acute myocardial infarction due to coronary occlusion.[20] The pain

may have the same characteristic features in both conditions; the slight elevation of temperature, sweating, fall of blood pressure, leukocytosis, and electrocardiographic changes may be identical in both. In such cases the presence of a widespread vasoconstriction has been proved experimentally and clinically; here, more than in any other condition the term vasospasm is justified. Following a hemorrhage sudden blindness due to spasm of the retinal arteries has been recorded. The picture of lower nephron nephrosis with anuria and of azotemia due to a disturbance of the renal blood flow is also well known.

The severe anginal pain in patients with hypertensive crisis with or without a pheochromocytoma represents another instance of coronary insufficiency which is certainly acute and so is the anginal pain observed in patients (even in children) with aortic insufficiency or aortic stenosis.

In all these situations the pathophysiologic state of coronary insufficiency exists, yet we would not be justified in using this term alone as a diagnosis, since the diagnosis of aortic stenosis with anginal pain, or hypertensive crisis with anginal pain, etc., tells us more.

Correct usage of medical terms is a fundamental necessity for clear thinking, for medical progress, and for correct management of the patient. We therefore believe that "coronary insufficiency" should not be considered a diagnosis any more than the term anginal pain. If the term "coronary insufficiency" is employed, it should be qualified. The cause and mechanism of the coronary insufficiency should be sought. The unqualified use of this term all too often gives the physician the false satisfaction that a diagnosis has been made. Important consequences follow. The patient suffering from a small acute infarction is not put at rest because he has "only coronary insufficiency." The prognosis is given as fair, since "only coronary insufficiency exists." Every patient complaining of prolonged anginal pain has tissue damage, which may be local or diffuse. Such patients need careful attention, even though they may not require prolonged bed rest and too marked restriction of their activity.

SUMMARY AND CONCLUSIONS

The original meaning of the term "coronary insufficiency" is discussed and the abuse of this term is illustrated by samples taken from the current medical literature. It is shown that the improper use of the term has led to great confusion.

It is proposed to limit this term to indicate a certain pathophysiologic state which may occur in a great variety of diseases. It does not involve a disease-entity. Therefore, this term should only be used with a qualifying description, indicating the specific type of coronary insufficiency present in an individual patient.

REFERENCES

1. Büchner, F.: Die Koronarinsuffizienz, Dresden, 1939, Theodor Steinkopf.
2. Boyd, L. J., and Scherf, D.: The Electrocardiogram After Mechanical Injury of the Inner Surface of the Heart, Bull. New York M. Coll. **3**:1, 1940, and Rev. argent. de cardiol. **7**:1, 1940.
3. Burak, M., and Scherf, D.: Angina Pectoris und Paroxysmale Tachykardie, Wien. Arch. f. inn. Med. **23**:475, 1933.

4. Burrett, J. B.: High Take-off of the S-T Segment Without Coronary Occlusion, Bull. New York M. Coll. **2**:121, 1939.
5. Danielopolu, D.: The Pathology and Surgical Treatment of Angina Pectoris, Brit. Med. J. **2**:553, 1924.
6. Freedberg, A. S., Blumgart, H. L., Zoll, P. M., and Schlesinger, M. J.: Coronary Failure, J. A. M. A. **138**:107, 1948.
7. Graybiel, A.: The Clinical Symptomatology of Coronary Insufficiency, Tr. Am. Coll. Cardiol. **1**:60, 1951.
8. Gregg, D. E.: Coronary Circulation in Health and Disease, Philadelphia, 1950, Lea & Febiger.
9. Hausner, E., and Scherf, D.: Ueber Angina-pectoris-Probleme, Ztschr. f. klin. Med. **126**:166, 1933.
10. Kossmann, C. E.: Electrocardiograms of Deceptive Form in Ventricular Hypertrophy, Circulation **8**:403, 1953.
11. Levy, R. L., and Bruenn, H. G.: Acute Fatal Coronary Insufficiency, J. A. M. A. **106**:1080, 1936.
12. Master, A. M., Dack, S., and Jaffe, H. L.: Nomenclature in Coronary Artery Disease, Mod. Concepts Cardiovas. Dis. **10**: 1941.
13. Master, A. M., Gubner, R., Dack, S., and Jaffe, H. L.: Differentiation of Acute Coronary Insufficiency With Myocardial Infarction From Coronary Occlusion, Arch. Int. Med. **67**:647, 1941.
14. Master, A. M., Jaffe, H. L., Dack, S., and Grishman, A.: Coronary Occlusion, Coronary Insufficiency, and Angina Pectoris, Am. Heart J. **27**:803, 1944.
15. Master, A. M., Dack, S., Grishman, A., Field, L. E., and Horn, H.: Acute Coronary Insufficiency: An Entity, J. Mt. Sinai Hosp. **14**:8, 1947.
16. Papp, C., and Smith, K. S.: Electrocardiographic Patterns in Slight Coronary Attacks, Brit. Heart J. **13**:17, 1951.
17. Questions and Answers: Modern Med., Oct., p. 33, 1953.
18. Rein, H.: Physiologie der Herzkranzgefässe, Ztschr. f. Biol. **92**:115, 1931.
19. Scherf, D., and Boyd, L. J.: Clinical Electrocardiography, Philadelphia, 1946, J. B. Lippincott Company, fig. 143, p. 164.
20. Scherf, D., and Klotz, S. D.: Electrocardiographic Changes After Acute Loss of Blood, Ann. Int. Med. **20**:438, 1944.
21. Scherf, D., and Schaffer, A. I.: The Electrocardiographic Exercise Test, Am. Heart J. **43**:927, 1952.
22. Thompson, S. A., and Plachta, A.: Experiences With Cardiopericardiopexy in the Treatment of Coronary Disease, J. A. M. A. **152**:678, 1953.

Announcement

A course in Electrocardiographic Interpretation for *graduate physicians* will be given at the Michael Reese Hospital, Chicago, Ill., by Louis N. Katz, M.D. (Director of the Cardiovascular Department, Medical Research Institute) and associates. The class will meet each day from 9:00 A.M. to 5:00 P.M. from August 2 through August 14, 1954.

Further information and a copy of the lecture schedule may be obtained upon application to Mrs. Rivian H. Lewin, Administrative Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16, Ill.

Book Reviews

LEISTUNGSSTEIGERUNG: LEISTUNG-ÜBERMÜDUNG-GESUNDERHALTUNG. By Dr. Max Hochrein and Dr. Irene Hochrein-Schleicher. Ed. 3, 283 pages with 53 figures and 20 tables. Stuttgart, 1953, George Thieme Verlag.

The book is essentially concerned with the relationship between work, fatigue and disease. Work, occupational and recreational, is the most common physiologic stress situation, and its effect on disease is an important problem for medicine and public health. Exploration of the broader aspects of the causes of disease is a comparatively new area, and there is a need for this type of book; however, this book does not quite fill the need.

Its greatest merit is that it has been written and thus brings these important problems to the attention of a wider professional public. It is a curious mixture of sound experimental work and much speculation. Unfortunately, the speculation is frequently presented in an authoritative and factual manner, and the nonmedical reader particularly will not be able to separate facts from speculation.

The incomplete coverage of pertinent literature particularly in areas outside of the experimental experience of the authors (circulation and respiration) is a serious defect. For instance, in the discussion of the role of nutrition (pp. 218-226) none of the controlled large scale experiments on the effect of diet on performance, carried out during and after the war in this country, are mentioned nor is the important cholesterol problem. Instead, one finds such statements as: "For many mental workers a diet rich in protein but low in fat and carbohydrates has been proven to be advantageous." Not only is there no valid experimental basis for such a statement, but it is even hard to design a diet which is high in protein and substantially lower in fat than the average diet. Many such examples could be given. As a whole, the treatment of the physiologic and psychologic background of work and fatigue (Chapter II) is not on a very competent level.

The main topic, however, is the importance of abnormal fatigue (Übermüdung) as a cause for the development of organic disease (Chapter III). "Normal" fatigue, resulting from work, is differentiated from abnormal or excessive fatigue (Übermüdung) from relatively small amounts of work and even in a resting condition. Since fatigue is a symptom of many diseased conditions, the authors reserve the term "Übermüdung" for patients who feel tired without any evidence of patent disease. The syndrome of neurocirculatory asthenia falls into this classification. Since normal as well as abnormal fatigue are essentially subjective phenomena, the differentiation is quite arbitrary. In order to obtain more objective criteria, the authors reproduced the state of excessive fatigue by experiments with 72 hours of sleep deprivation in two normal subjects. It is questionable how far the similarity goes, but the more serious objection is the generalization made on the basis of only two subjects. Unfortunately, the author is not aware of the larger American material (Ivy, A. C., and Goetzl, F. R., War Med. 3:60, 1943; Tyler, D. B., Federation Proc. 6:218, 1947).

The experimental results, however, are of definite interest, particularly the increased reflex response of peripheral circulation (plethysmographically recorded) to thermal stimuli in the state of Übermüdung; in some more advanced cases even a paradoxic response (decrease of peripheral blood flow on heat application) is observed.

The authors maintain that functional disturbances which characterize the state of "Übermüdung" ultimately result in organic disorders, and this thought is applied to diseases of the heart, central nervous system, lungs, intestinal tract, liver, eyes, etc. We limit this review to circulatory and respiratory disease. It is maintained that coronary insufficiency (angina pectoris) starts as an increased reflex irritability of the coronary arteries. The correlation between anatomic changes and angina attacks is poor. It is claimed that 40 per cent of the patients with myocardial infarct do not have pain, and only 15 per cent of the patients with coronary atherosclerosis have angina pectoris. It is assumed that coronary spasm is the primary disturbance, and vascular degeneration the secondary event. Thus, ultimately, an attack of coronary spasm

might produce myocardial infarct. Therefore, physical work is listed as the Number 1 cause for myocardial infarct. However, Master (J. A. M. A. **128**:775, 1945) has convincingly shown that there is no correlation between physical work and the occurrence of myocardial infarct, but this material has escaped the authors. The existence of coronary spasm is presented as fact, while it is, at best, a debatable hypothesis.

The percentage of silent infarcts, in the experience of the authors, is excessively high and more precise information about the material is needed. Possibly, microscopic necrotic areas were considered as infarcts. In another place it is claimed that 35 to 40 per cent of all apparently cardiac troubles such as palpitation, chest pain, etc., actually are due to intestinal disorders. Such loose statements may easily produce confusion in nonmedical readers.

In regard to pulmonary diseases, it is claimed that the initial functional disturbance in the pulmonary circulation is a short circuit of the greater part of the pulmonary blood flow through arteriovenous anastomoses ("pulmonal dystony"). This produces dyspnea at comparatively low work loads, while in more severe exertion the dyspnea disappears because of the opening of alveolar capillaries. Ultimately, bronchial asthma and pulmonal emphysema may develop. The diagnosis of such "pulmonal dystony" is difficult in the first place, and the causal relationship to asthma and emphysema has still to be demonstrated.

The last part of the book is devoted to the therapy of fatigue but cannot be discussed in the limited space of this review.

A minor objection is that some authors are quoted in the text but not included in the list of references.

The book contains much interesting material and is stimulating, but much of the stimulation arises from the temptation to challenge many of the statements and conclusions.

E. S.

HYPERTENSIVE DISEASES: CAUSES AND CONTROL. By Henry A. Schroeder, M.D. 610 pages. Philadelphia, 1953, Lea & Febiger. Price $10.00.

This is an interesting and provocative book concerning arterial hypertension. Dr. Schroeder has attempted to supply a great deal of information about essential hypertension, paying particular attention to those aspects which tend to lend support to his concept of pathogenesis. He has also reviewed and organized a great deal of information about other varieties of hypertension. Unfortunately, all of this material is considerably colored by Dr. Schroeder's personal point of view.

The sections on therapy of hypertensive disease are dominated by Dr. Schroeder's theory that hydralazine is a specific weapon against a pressor substance in the blood of certain hypertensives. He also believes that his particular combination of hydralazine and hexamethonium (Hyphex) is superior to any other regimen currently available for most hypertensive individuals. Since few physicians familiar with the treatment of essential hypertension would agree with Dr. Schroeder's views on this subject without definite reservations, his emphasis on this point weakens the entire commentary. Also, his complete omission of consideration of other drugs and therapeutic weapons for the treatment of arterial hypertension does not seem to be practical in a book which, to a certain extent, attempts to span the subject.

If one agrees with Dr. Schroeder's concept as to the etiology and treatment of agnogenic hypertension, this book is valuable for practical information. If one disagrees with the general concept, it is interesting to read the book to see how his theory is organized and defended. However, physicians who have not paid special attention to the problems of arterial hypertension may be considerably misled by some of Dr. Schroeder's statements. Despite the fact that this book should be taken with a grain of salt (this seems justifiable when speaking of hypertension), it has considerable value to most physicians interested in hypertensive disease. Its main limitation is that it attempts to defend a theory which at the moment is little more than pure speculation.

W.M.K.

INDEX TO VOLUME 47

AUTHORS INDEX

A

ABHYANKAR, R. N. (*See* Rahman, Abhyankar, and Ali), 394

ALBRIGHT, LOUIS F., AND BROWN, FRANK J. Acute myocardial infarction associated with acute porphyria, 108

ALI, TAHIR. (*See* Rahman, Abhyankar, and Ali), 394

ALLENSTEIN, B. J. (*See* Elek, Allenstein, Griffith, Cosby, and Levinson), 369

——. (*See* Elek, Allenstein, Kornbluth, Griffith, and Levinson), 477

AMORIM, IVAN DE. (*See* Tranchesi, Carral, Amorim, and Peñaloza), 664

ANDERSON, WILLIAM H., URBACH, KARL, AND DOERNER, ALEXANDER A. Ballistic respiratory variation as measured by the electromagnetic ballistocardiograph, 15

B

BAHN, ROBERT C., SANES, SAMUEL, JUVELIER, BERNARD W., AND URBAN, STANLEY T. Presubclavian coarctation of the aorta, 444

BAILEY, CHARLES P. (*See* Goldberg, Bakst, and Bailey), 527

——. (*See* Trace, Bailey, and Wendkos), 613

BAKER, LYLE A. (*See* Kaplan, Puestow, Baker, and Kruger), 824

BAKKEN, EARL E. (*See* Simonson, Schmitt, Dahl, Fry, and Bakken), 122

BAKST, ALVIN A. (*See* Goldberg, Bakst, and Bailey), 527

BARSOUM, G. S., AND KENAWY, M. R. The spasmolytic action of "soluble khellin-Nokhel," 297

BIÖRCK, GUNNAR. (*See* Thorson, Biörck, Björkman, and Waldenström), 795

BJÖRK, VIKING OLOV, MALMSTRÖM, GUNNAR, AND UGGLA, LARS G. Left atrial and pulmonary "capillary" pressure curves during Valsalva's experiment, 635

BJÖRKMAN, GUNNAR. (*See* Thorson, Biörck, Björkman, and Waldenström), 795

BLAKE, H. A. (*See* Goyette, Farinacci, Forsee, and Blake), 645

BOIKAN, WILLIAM S., AND GUNNAR, ROLF M. Aberrant conduction in supraventricular extrasystoles eliminated by exercise, 626

BOYD, G. S. (*See* Oliver and Boyd), 348

BRIGGS, JOHN FRANCIS, AND HOLT, JOHN. Prolonged survival following perforation of the interventricular septum as a result of a myocardial infarction, 926

BROWN, FRANK J. (*See* Albright and Brown), 108

BRUCE, ROBERT A., AND HAGEN, JOHN M. V. Anomaly of total pulmonary venous connection, 785

BUCKINGHAM, WILLIAM B. (*See* Sutton, Sutton, Hinkens, Buckingham, and Rondinelli), 67

BURCH, G. E., and ROMNEY, R. B. Functional anatomy and "throttle valve" action of the pulmonary veins, 58

BURCHELL, HOWARD B. (*See* Mann and Burchell), 504

C

CACCESE, A. (*See* Kelly, Caccese, Ortiz-Marquez, and Taubman), 30

CARRAL, RAFAEL. (*See* Tranchesi, Carral, Amorim, and Peñaloza), 664

CHAPMAN, DON W. (*See* Livesay, Moyer, and Chapman), 745

CHAPMAN, JAMES E. (*See* Woldow, Chapman, and Evans), 568

CHENG, JOHN T. O. (*See* Swisher, Wedell, Cheng, Sutton, and Sutton), 449

CISNEROS, FERNANDO. (*See* Puech, Esclavissat, Sodi-Pallares and Cisneros), 174

COHN, ISIDOR. (*See* Richards and Cohn), 313

CORDEIRO, ARSÉNIO. Right ventricular stenosis of the Bernheim type in a case of septal infarction, 112

COSBY, RICHARD S. (*See* Elek, Allenstein, Griffith, Cosby, and Levinson), 369

D

DAHL, JAMES. (*See* Simonson, Schmitt, Dahl, Fry, and Bakken), 122

DENTON, CLARENCE. (*See* Wakim, Denton, and Essex), 77

DICKERSON, ROBERT B. Performance of angiocardiography and cardiac catheterization as a combined procedure, 252

DIMOND, E. GREY, AND JONES, T. REID. Pulmonary artery thrombosis simulating pulmonic valve stenosis with patent foramen ovale, 105

DOANE, JOHN H., JR. (*See* Shuman, Learner, and Doane), 737

DOERNER, ALEXANDER A. (*See* Anderson, Urbach, and Doerner), 15

DORBECKER, NARNO. (*See* Neri, Villagordoa, Moros, and Dorbecker), 818

DRESSLER, WILLIAM. (*See* Roesler and Dressler), 520

DUNN, JAMES J., SARRELL, WARREN, AND FRANKLIN, R. B. The Wolff-Parkinson-White syndrome associated with paroxysmal ventricular tachycardia, 462

DURRER, D., AND VAN DER TWEEL, L. H. Spread of activation in the left ventricular wall of the dog. II, 192

E

ELEK, STEPHEN R., ALLENSTEIN, B. J., GRIFFITH, GEORGE C., COSBY, RICHARD S., AND LEVINSON, DAVID C. A correlation of the spatial vectorcardiogram with right ventricular hypertrophy, 369

——, ——, KORNBLUTH, A. W., GRIFFITH, GEORGE C., AND LEVINSON, DAVID C. The spatial vectorcardiogram in myocardial infarction typified by prominent R waves in leads aV_R and V_1, 477

ESCLAVISSAT, MICHEL. (*See* Puech, Esclavissat, Sodi-Pallares, and Cisneros), 174

ESSELLIER, A. F. (*See* Löffler, Essellier, and Forster), 898

ESSEX, HIRAM E. (*See* Wakim, Denton, and Essex), 77

EVANS, JOHN M. (*See* Woldow, Chapman, and Evans), 568

F

FALHOLT, WALTHER. (*See* Gøtzsche and Falholt), 587

FARINACCI, C. J. (*See* Goyette, Farinacci, Forsee, and Blake), 645

FORSEE, J. H. (*See* Goyette, Farinacci, Forsee, and Blake), 645

FORSTER, G. (*See* Löffler, Essellier, and Forster), 898

FRANK, ERNEST. The image surface of a homogeneous torso, 757

FRANKLIN, R. B. (*See* Dunn, Sarrell, and Franklin), 462

——. (*See* Morris and Franklin), 919

FRY, DONALD. (*See* Simonson, Schmitt, Dahl, Fry, and Bakken), 122

G

GEAR, J. H. (*See* van Lingen, Gear, Whidborne, and Lister), 560

GECKELER, GEORGE D. (*See* Likoff, Geckeler, and Gregory), 619

GEDDES, L. A. (*See* Sekelj, Geddes, and Hoff), 95

GIDDINGS, LANE W. (*See* Lehmus, Sundquist, and Giddings), 470

GILLIS, J. G., AND WALTERS, M. B. Acute isolated myocarditis simulating coronary occlusion, 117

GLOTZER, SOL. Electrocardiographic changes during sensitivity reaction to penicillin, 300

GOLBEY, MAURICE. (*See* Scherf and Golbey), 928

GOLDBERG, HARRY, BAKST, ALVIN A., AND BAILEY, CHARLES P. The dynamics of aortic valvular disease, 527

GØTZSCHE, HENNING, AND FALHOLT, WALTHER. Ebstein's anomaly of the tricuspid valve, 587

GOYETTE, E. M., FARINACCI, C. J., FORSEE, J. H., AND BLAKE, H. A. The clinicopathologic correlation of lung biopsies in mitral stenosis, 645

GRAY, FRANK D., JR., AND GRAY, FRIEDA G. The effect of lanatoside C on the circulatory and ventilatory changes of chronic rheumatic heart disease with mitral stenosis, 282

GRAY, FRIEDA G. (*See* Gray and Gray), 282

GREGORY, JOHN E. (*See* Likoff, Geckeler, and Gregory), 619

GRIFFITH, GEORGE C. (*See* Elek, Allenstein, Griffith, Cosby, and Levinson), 369

——. (*See* Elek, Allenstein, Kornbluth, Griffith, and Levinson), 477

GROSS, DESIDERIO. The duration of the T wave and its relation to the cardiac rate in healthy adults, 514

GUNNAR, ROLF M. (*See* Boikan and Gunnar), 626

H

HAGEN, JOHN M. V. (*See* Bruce and Hagen), 785

HANSEN, JAMES E. (*See* Miller, Hansen, and Pollock), 453

HELLERSTEIN, HERMAN K., SHAW, DENMAN, AND SANO, TOYOMI. Dissection of the vectorcardiogram: differential vectorcardiography, 887

HERNANDEZ, F. A. (*See* Saslaw, Ross, and Hernandez), 580

HINKENS, GEORGE F. (*See* Sutton, Sutton, Hinkens, Buckingham, and Rondinelli), 67

HOFF, H. E. (*See* Sekelj, Geddes, and Hoff), 95

HOLT, JOHN. (*See* Briggs and Holt), 926

HOOVER, M. P., AND MANNING, G. W. The effects of cortisone and ACTH on artificially induced cardiac infarction in the dog, 343

HULL, CATHERINE. (*See* Jacobson, Lipkis, and Hull), 860

J

JACKSON, ALBERT, AND SLAVIN, MANUEL. "Primary" amyloidosis, 839

JACOBSON, GEORGE, LIPKIS, MAURICE L., AND HULL, CATHERINE. The cardiovascular aspects of the Los Angeles County mass chest x-ray survey, 860

JERVELL, ANTON. Pulseless disease, 780

JONES, T. REID. (*See* Dimond and Jones), 105

JOOS, HOWARD A. (*See* Yu, Simpson, Lovejoy, Joos, and Nye), 330

JUVELIER, BERNARD W. (*See* Bahn, Sanes, Juvelier, and Urban), 444

JUVENELLE, ANDRE A., LIND, JOHN, AND WEGELIUS, CARL. A new method of extracorporeal circulation, 692

K

KAPLAN, ERVIN, PUESTOW, ROBERT C., BAKER, LYLE A., AND KRUGER, SAM. Blood volume in congestive heart failure as determined with iodinated human serum albumin, 824

KELLY, J. J., JR., CACCESE, A., ORTIZ-MARQUEZ, J., AND TAUBMAN, F. The effects of cigarette smoking on the ballistocardiograms of high school youths, 30

KENAWY, M. R. (*See* Barsoum and Kenawy), 297

KENNAMER, REXFORD, AND PRINZMETAL, MYRON. Depolarization of the ventricle with bundle branch block. Studies on the mechanism of ventricular activity. X, 769

KESSELMAN, RUSSELL H. A new synthesis of some of the physical foundations of clinical electrocardiography, 360

KITAMURA, KAZUO. (*See* Yamakawa, Shionoya, Kitamura, Nagai, Yamamoto, and Ohta), 424

KORNBLUTH, A. W. (*See* Elek, Allenstein, Kornbluth, Griffith, and Levinson), 477

KORY, ROSS C. (*See* Roehm, Kory, Mabe, Townes, and Meneely), 204

KRUGER, SAM. (*See* Kaplan, Puestow, Baker, and Kruger), 824

L

LAMBERT, JOSEPH. Value of additional thoracic and abdominal unipolar leads for diagnosis of the location and extension of myocardial infarctions, 40

LANDALE, DONALD G. (*See* Schlappi and Landale), 432

LEARNER, NORMAN. (*See* Shuman, Learner, and Doane), 737

LEHMUS, HAROLD J., SUNDQUIST, ALFRED B., AND GIDDINGS, LANE W. Coronary thrombosis with myocardial infarction secondary to nonpenetrating injury of the chest wall, 470

LEVINSON, DAVID C. (*See* Elek, Allenstein, Griffith, Cosby, and Levinson), 369

——. (*See* Elek, Allenstein, Kornbluth, Griffith, and Levinson), 477

LIKOFF, WILLIAM, GECKELER, GEORGE D., AND, GREGORY, JOHN E. Functional mitral stenosis produced by an intra-atrial tumor, 619

LIND, JOHN. (*See* Juvenelle, Lind, and Wegelius), 692

LIPKIS, MAURICE L. (*See* Jacobson, Lipkis, and Hull), 860

LISTER, MARGARET L. (*See* van Lingen, Gear, Whidborne, and Lister), 560

LIVESAY, W. R., MOYER, JOHN H., AND CHAPMAN, DON W. The cardiovascular and renal hemodynamic effects of Aramine, 745

LÖFFLER, W., ESSELLIER, A. F., AND FORSTER, G. Acetyl-digitoxin, 898

LOSNER, SAMUEL. Ballistoscope recording with the aid of an asymmetrical shutter, 34

——. (*See* Volk and Losner), 658

LOVEJOY, FRANK W., JR. (*See* Yu, Simpson, Lovejoy, Joos, and Nye), 330

LOWENSTEIN, FRANK W. Some epidemiological aspects of blood pressure and its relationship to diet and constitution with particular consideration of the Chinese, 874

M

MABE, ROBERT E. (*See* Roehm, Kory, Mabe, Townes, and Meneely), 204

MCKIM, J. S., AND WIGLESWORTH, F. W. Absence of the left pulmonary artery, 845

MALMSTRÖM, GUNNAR. (*See* Björk, Malmström, and Uggla), 635

MANN, RICHARD H., AND BURCHELL, HOWARD B. The significance of T-wave inversion in sinus beats following ventricular extrasystoles, 504

MANNING, G. W. (*See* Hoover and Manning), 343

MASTER, ARTHUR M. The etiology of cardiac enlargement in coronary occlusion, hypertension, and coronary artery disease, 321

MATHERS, JAMES A. L. (*See* Nickerson and Mathers), 1

MENEELY, GEORGE R. (*See* Roehm, Kory, Mabe, Townes, and Meneely), 204

MILLER, GEORGE, HANSEN, JAMES E., AND POLLOCK, BYRON E. Staphylococcus endocarditis, 453

MOROS, GUSTAVO. (*See* Neri, Villagordoa, Moros, and Dorbecker), 818

MORRIS, GLENN M., AND FRANKLIN, R. B. Ventricular tachycardia due to idiopathic pericarditis controlled by simultaneous intravenous procaine amide and quinidine, 919

MOTTU, TH. Artificial reduction of the heart effort, 270

MOYER, JOHN H., AND SNYDER, HARVEY B. The cerebral hemodynamic response to the xanthine compound, Parephyllin (diethyl-aminoethyl theophylline hydrochloride), 912

——. (*See* Livesay, Moyer, and Chapman), 745

MUSTAKALLIO, KIMMO K., AND SARAJAS, H. S. SAMULI. Some aspects of scleroderma heart disease, 437

N

NADAS, ALEXANDER S. (*See* Reinhold and Nadas), 405

NAGAI, TOICHI. (*See* Yamakawa, Shionoya, Kitamura, Nagai, Yamamoto, and Ohta), 424

NERI, RAFAEL JOSÉ, VILLAGORDOA, GUILLERMO, MOROS, GUSTAVO, AND DORBECKER, NARNO. Pulmonary circulation time, elbow-left ventricle and elbow-right ventricle circulation times, obtained by means of fluorodensography with radiopaque substance, 818

NICKERSON, JOHN L., AND MATHERS, JAMES A. L. A study of the physical properties of the ballistocardiograph, 1

NYE, ROBERT E., JR. (*See* Yu, Simpson, Lovejoy, Joos, and Nye), 330

O

OHTA, SATOSHI. (*See* Yamakawa, Shionoya, Kitamura, Nagai, Yamamoto, and Ohta), 424

OLIVER, M. F., AND BOYD, G. S. The effect of estrogens on the plasma lipids in coronary artery disease, 348
ORTIZ-MARQUEZ, J. (*See* Kelly, Caccese, Ortiz-Marquez, and Taubman), 30

P

PEDERSEN, ASGER, AND THERKELSEN, F. Cor triatriatum: a rare malformation of the heart, probably amenable to surgery, 676
PEÑALOZA, DANTE. (*See* Tranchesi, Carral, Amorim, and Peñaloza), 664
PINES, IGNACY. The influence of khellin (Visammin) upon the electrocardiogram, 487
POLLOCK, BYRON E. (*See* Miller, Hansen, and Pollock), 453
POWELL, GEORGE M. (*See* Smyth and Powell), 218
PRAKASH, RAVI. The heart of the rat with special reference to the conducting system, 241
PRESCOTT, E. J. (*See* Weisman, Weisman, and Prescott), 84
PRINZMETAL, MYRON. (*See* Kennamer and Prinzmetal), 769
PUECH, PAUL, ESCLAVISSAT, MICHEL, SODI-PALLARES, DEMETRIO, AND CISNEROS, FERNANDO. Normal auricular activation in the dog's heart, 174
PUESTOW, ROBERT C. (*See* Kaplan, Puestow, Baker, and Kruger), 824

R

RAHMAN, S. A., ABHYANKAR, R. N., AND ALI, TAHIR. Effect of cooling the anterior chest wall on the T wave of the electrocardiogram, 394
REINHOLD, JOHN D. L., AND NADAS, ALEXANDER S. The role of auscultation in the diagnosis of congenital heart disease, 405
RICHARDS, DICKINSON W., AND COHN, ISIDOR. Interventricular septal defect, pulmonary artery aneurysm with thrombosis, "cyanose tardive," and paradoxical systemic arterial embolizations, 313
RICHMAN, J. L. (*See* Wolff, Richman, and Soffe), 161
RICHMAN, JUSTIN L., AND WOLFF, LOUIS. Left bundle branch block masquerading as right bundle branch block, 383
ROEHM, DAN C., KORY, ROSS C., MABE, ROBERT E., TOWNES, ALEXANDER S., AND MENEELY, GEORGE R. Duration of the Q-T interval during the anoxemia test, 204
ROESLER, HUGO, AND DRESSLER, WILLIAM. Transient electrocardiographic changes identical with those of acute myocardial infarction accompanying attacks of angina pectoris, 520
ROMNEY, R. B. (*See* Burch and Romney), 58
RONDINELLI, RAYMOND. (*See* Sutton, Sutton, Hinkens, Buckingham, and Rondinelli), 67
ROSS, BERNARD D. (*See* Saslaw, Ross, and Hernandez), 580
RUSSEK, ALLEN S. (*See* Russek, Zohman, and Russek), 653
RUSSEK, HENRY I., ZOHMAN, BURTON L., AND RUSSEK, ALLEN S. Risk of thromboembolic complications from cortisone therapy, 653

S

SANES, SAMUEL. (*See* Bahn, Sanes, Juvelier, and Urban), 444
SANO, TOYOMI. (*See* Hellerstein, Shaw, and Sano), 887
SARAJAS, H. S. SAMULI. (*See* Mustakallio and Sarajas), 437
SARRELL, WARREN. (*See* Dunn, Sarrell, and Franklin), 462
SASLAW, MILTON S., ROSS, BERNARD D., AND HERNANDEZ, F. A. Rheumatic heart disease in native-born Floridians and non-Floridians, 580
SCHERF, DAVID, AND GOLBEY, MAURICE. An evaluation of the term "coronary insufficiency," 928
SCHLAPPI, JOHN C., AND LANDALE, DONALD G. Perforation of the infarcted interventricular septum, 432
SCHMITT, OTTO H. (*See* Simonson, Schmitt, Dahl, Fry, and Bakken), 122
SEKELJ, P., GEDDES, L. A., AND HOFF, H. E. A line-operated direct-coupled electrocardiograph, 95
SHAW, DENMAN. (*See* Hellerstein, Shaw, and Sano), 887
SHIONOYA, YASUO. (*See* Yamakawa, Shionoya, Kitamura, Nagai, Yamamoto, and Ohta), 424
SHUMAN, CHARLES R., LEARNER, NORMAN, AND DOANE, JOHN H., JR. The effect of ganglion blocking agents in congestive heart failure, 737
SIMONSON, ERNST, SCHMITT, OTTO H., DAHL, JAMES, FRY, DONALD, AND BAKKEN, EARL E. The theoretical and experimental bases of the frontal plane ventricular gradient and its spatial counterpart, 122
SIMPSON, JOHN H. (*See* Yu, Simpson, Lovejoy, Joos, and Nye), 330
SLAVIN, MANUEL. (*See* Jackson and Slavin), 839
SMYTH, ALBERT G., AND POWELL, GEORGE M. The electrocardiogram in hemorrhagic fever, 218
SNYDER, HARVEY B. (*See* Moyer and Snyder), 912
SODI-PALLARES, DEMETRIO. (*See* Puech, Esclavissat, Sodi-Pallares, and Cisneros), 174
SOFFE, A. M. (*See* Wolff, Richman, and Soffe), 161
SUNDQUIST, ALFRED B. (*See* Lehmus, Sundquist, and Giddings), 470
SUTTON, DON C. (*See* Swisher, Wedell, Cheng, Sutton, and Sutton), 449

——, SUTTON, GEORGE C., HINKENS, GEORGE F., BUCKINGHAM, WILLIAM B., AND RONDINELLI, RAYMOND. Studies on whole blood and muscle creatine levels: effect of systemic and local anoxia, of cardiac failure and compensation, and of alpha-tocopherol administration, 67

SUTTON, GEORGE C. (*See* Sutton, Sutton, Hinkens, Buckingham, and Rondinelli), 67

——. (*See* Swisher, Wedell, Cheng, Sutton, and Sutton), 449

SWISHER, WILLIAM P., WEDELL, HAROLD G., CHENG, JOHN T. O., SUTTON, GEORGE C., AND SUTTON, DON C. Studies of quinidine plasma levels and rate of decline following cessation of quinidine administration, 449

T

TAUBMAN, F. (*See* Kelly, Caccese, Ortiz-Marquez, and Taubman), 30

THERKELSEN, F. (*See* Pedersen and Therkelsen), 676

THORSON, ÅKE, BIÖRCK, GUNNAR, BJÖRKMAN, GUNNAR, AND WALDENSTRÖM, JAN. Malignant carcinoid of the small intestine with metastases to the liver, valvular disease of the right side of the heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction and an unusual type of cyanosis, 795

TOWNES, ALEXANDER S. (*See* Roehm, Kory, Mabe, Townes, and Meneely), 204

TOWNSEND, CHARLES E. (*See* Zimdahl and Townsend), 304

TRACE, HERBERT D., BAILEY, CHARLES P., AND WENDKOS, MARTIN H. Tricuspid valve commissurotomy with a one-year follow-up, 613

TRANCHESI, JOÃO, CARRAL, RAFAEL, AMORIM, IVAN DE, AND PEÑALOZA, DANTE. The clinical diagnosis of bicuspid aortic valve, 664

U

UGGLA, LARS G. (*See* Björk, Malmström, and Uggla), 635

URBACH, KARL. (*See* Anderson, Urbach, and Doerner), 15

URBAN, STANLEY T. (*See* Bahn, Sanes, Juvelier, and Urban), 444

V

VAN LINGEN, B., GEAR, J. H., WHIDBORNE, JOANNA, AND LISTER, MARGARET L. The ballistocardiogram in aortic stenosis, 560

VAN DER TWEEL, L. H. (*See* Durrer and van der Tweel), 192

VESELL, HARRY. Congenital heart disease and acute myocardial infarction, 604

VILLAGORDOA, GUILLERMO. (*See* Neri, Villagordoa, Moros, and Dorbecker), 818

VOLK, BRUNO W., AND LOSNER, SAMUEL. The erythrocyte sedimentation rate in hemoconcentration associated with acute myocardial infarction, 658

W

WAKIM, KHALIL G., DENTON, CLARENCE, AND ESSEX, HIRAM E. Certain cardiovascular effects of vasopressin (Pitressin), 77

WALDENSTRÖM, JAN. (*See* Thorson, Biörck, Björkman, and Waldenström), 795

WALTERS, M. B. (*See* Gillis and Walters), 117

WEDELL, HAROLD G. (*See* Swisher, Wedell, Cheng, Sutton, and Sutton), 449

WEGELIUS, CARL. (*See* Juvenelle, Lind, and Wegelius), 592

WEISMAN, S. A., WEISMAN, S. J., AND PRESCOTT, E. J. Analeptic effects of Aranthol in vasomotor depression induced by quinidine, 84

WEISMAN, S. J. (*See* Weisman, Weisman, and Prescott), 84

WELLS, PHILIP V. An improved flarimeter, 102

WENDKOS, MARTIN H. (*See* Trace, Bailey, and Wendkos), 613

WHIDBORNE, JOANNA. (*See* van Lingen, Gear, Whidborne, and Lister), 560

WIGLESWORTH, F. W. (*See* McKim and Wiglesworth), 845

WOLDOW, ASHER, CHAPMAN, JAMES E., AND EVANS, JOHN M. Fat tolerance in subjects with atherosclerosis: heparin effects upon lipemia, lipoproteins, and gamma globulin, 568

WOLFF, L., RICHMAN, J. L., AND SOFFE, A. M. The effect of heart position and rotation on the cardiac vector: an experimental study, 161

WOLFF, LOUIS. (*See* Richman and Wolff), 383

Y

YAMAKAWA, KUNIO, SHIONOYA, YASUO, KITAMURA, KAZUO, NAGAI, TOICHI, YAMAMOTO, TAKAYA, AND OHTA, SATOSHI. Intracardiac phonocardiography, 424

YAMAMOTO, TAKAYA. (*See* Yamakawa, Shionoya, Kitamura, Nagai, Yamamoto, and Ohta), 424

YU, PAUL N. G., SIMPSON, JOHN H., LOVEJOY, FRANK W., JR., JOOS, HOWARD A., AND NYE, ROBERT E., JR. Studies of pulmonary hypertension. IV, 330

Z

ZIMDAHL, WALTER T., AND TOWNSEND, CHARLES E. Bidirectional ventricular tachycardia due to digitalis poisoning, 304

ZOHMAN, BURTON L. (*See* Russek, Zohman, and Russek), 653

ZUMOFF, BARNETT. Temporary atrioventricular conduction disturbance associated with ingestion of veratrum viride, 630

SUBJECT INDEX

A

Abdominal unipolar leads, thoracic and additional, value of, for diagnosis of location and extension of myocardial infarctions (Lambert), 40

Aberrant conduction in supraventricular extrasystoles eliminated by exercise (Boikan and Gunnar), 626

Acetyl-digitoxin (Löffler et al.), 887
effect of treatment with, on venous pressure, circulation time, and vital capacity in patients with heart failure (Table IV) (Löffler et al.), 904

ACTH, effects of cortisone and, on artificially induced cardiac infarction in dog (Hoover and Manning), 343

Activation, atrial, right (Puech et al.), 177
auricular, abnormal, considerations on (Puech et al.), 189
left (Puech et al.), 181
normal, in dog's heart (Puech et al.), 174
conditions at epicardial surface of left ventricle, investigation of (Durrer and van der Tweel), 193
process, general, study of (Puech et al.), 183
septum, interatrial (Puech et al.), 183
spread of, in left ventricular wall of dog. II (Durrer and van der Tweel), 192

Albumin, serum, human, iodinated, blood volume in congestive heart failure as determined with (Kaplan et al.), 824

Alpha-tocopherol administration, effect of systemic and local anoxia, of cardiac failure and compensation, and; studies on whole blood and muscle creatine levels (Sutton et al.), 67

Aminophylline, response of Parephyllin as compared to, in various types of patients studied (Table III) (Moyer and Snyder), 916

Amyloidosis, "primary" (Jackson and Slavin), 839

Anatomy, functional, and "throttle valve" action of pulmonary veins (Burch and Romney), 58

Aneurysm, pulmonary artery, with thrombosis, interventricular septal defect, "cyanose tardive," and paradoxical systemic arterial embolizations (Richards and Cohn), 313

Angina pectoris, transient electrocardiographic changes identical with those of acute myocardial infarction accompanying attacks of (Roesler and Dressler), 520

Angiocardiography and cardiac catheterization, performance of, as combined procedure (Dickerson), 252

Angioquimografia, 474 (B. Rev.)

Announcements, 157, 318, 475, 476, 794

Anomaly, Ebstein's, of tricuspid valve (Gøtzsche and Falholt), 587

Anoxemia test, duration of Q-T interval during (Roehm et al.), 204

Anoxia, systemic and local, effect of cardiac failure and compensation, of alpha-tocopherol administration, and; studies on whole blood and muscle creatine levels (Sutton et al.), 67

Aorta, presubclavian coarctation of (Bahn et al.), 444

Aortic stenosis, ballistocardiogram in (van Lingen et al.), 560
valve, bicuspid, clinical diagnosis of (Tranchesi et al.), 664
valvular disease, correlation of clinical and physiologic findings in patients with (Goldberg et al.), 555
dynamics of (Goldberg et al.), 527

Aramine, cardiovascular and renal hemodynamic effects of (Livesay et al.), 745
effect of continuous intravenous infusion of, on creatinine clearance, renal plasma flow, and hematocrit (Table IB) (Livesay et al.), 749
infusion of, on urinary excretion of water and electrolytes (Table II) (Livesay et al.), 751
renal hemodynamic and blood pressure response to continuous intravenous infusion of (Table IA) (Livesay et al.), 748

Aranthol, analeptic effects of, in vasomotor depression induced by quinidine (Weisman et al.), 84

Arterial embolizations, systemic, paradoxical, interventricular septal defect, pulmonary artery aneurysm with thrombosis, "cyanose tardive," and (Richards and Cohn), 313

Artery, coronary, disease, effect of estrogens on plasma lipids in (Oliver and Boyd), 348
etiology of cardiac enlargement in coronary occlusion, hypertension, and (Master), 321
pulmonary, left, absence of (McKim and Wiglesworth), 845
thrombosis, simulating pulmonic valve stenosis with patent foramen ovale (Dimond and Jones), 105

Asymmetrical shutter, ballistoscope recording with aid of (Losner), 34

Atherosclerosis, fat tolerance in subjects with: heparin effects upon lipemia, lipoproteins, and gamma globulin (Woldow et al.), 568

Atrial, left, and pulmonary "capillary" pressure curves during Valsalva's experiment (Björk et al.), 635

Atriovenous junction, gross appearance of (Burch and Romney), 61

Atrioventricular conduction disturbance, temporary, associated with ingestion of veratrum viride (Zumoff), 630

Auricular activation, abnormal, considerations on (Puech et al.), 189
normal, in dog's heart (Puech et al.), 174

Auscultation, role of, in diagnosis of congenital heart disease (Reinhold and Nadas), 405

B

Balistocardiografia clinica, 320 (B. Rev.)
Ballistic respiratory variation as measured by electromagnetic ballistocardiograph (Anderson et al.), 15
Ballistocardiogram, 319 (B. Rev.)
in aortic stenosis (van Lingen et al.), 560
Ballistocardiograms of high school youths, effects of cigarette smoking on (Kelly et al.), 30
Ballistocardiograph, electromagnetic, ballistic respiratory variation as measured by (Anderson et al.), 15
study of physical properties of (Nickerson and Mathers), 1
Ballistoscope, description of (Losner), 35
recording with aid of asymmetrical shutter (Losner), 34
Bernheim type, right ventricular stenosis of, in case of septal infarction (Cordeiro), 112
Bicuspid aortic valve, clinical diagnosis of (Tranchesi et al.), 664
Block, bundle branch, depolarization of ventricle with (Kennamer and Prinzmetal), 769
Blocking, ganglion, agents, effect of, in congestive heart failure (Shuman et al.), 737
Blood pressure and pulse rate, behavior of, during experiments; extracorporeal circulation (Juvenelle et al.), 698
in persons 65 and over, 157
levels, mean systolic, comparison of, in several groups of Chinese and American students (Table IV) (Lowenstein), 880
response, renal hemodynamic and, to continuous intravenous infusion of Aramine (Table IA) (Livesay et al.), 748
some epidemiologic aspects of, and its relationship to diet and constitution with particular consideration of Chinese (Lowenstein), 874
volume in congestive heart failure as determined with iodinated human serum albumin (Kaplan et al.), 824
whole, and muscle creatine levels, studies on: effect of systemic and local anoxia, of cardiac failure and compensation, and of alpha-tocopherol administration (Sutton et al.), 67
Blutkreislaufes, das Strömungsgesetz des, 634 (B. Rev.)
Book reviews, 154, 319, 474, 634, 793, 935
Bronchoconstriction, malignant carcinoid of small intestine with metastases to liver, valvular disease of right side of heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, and unusual type of cyanosis (Thorson et al.), 795
Bundle branch block, depolarization of ventricle with (Kennamer and Prinzmetal), 769
Bundle Branch Block—Cont'd
left (Wolff et al.), 165
masquerading as right bundle branch block (Richman and Wolff), 383
right, incomplete, complicated by right ventricular hypertrophy (Wolff et al.), 171
uncomplicated (Wolff et al.), 165

C

Capacity, vital, effect of treatment with acetyldigitoxin on venous pressure, circulation time, and in patients with heart failure (Table IV) (Löffler et al.), 904
"Capillary" pressure curves, left atrial and pulmonary, during Valsalva's experiment (Björk et al.), 635
Carbon dioxide, effect of Parephyllin (R-3588) on cerebral blood oxygen and (Table II) (Moyer and Snyder), 915
Carcinoid, malignant, of small intestine with metastases to liver, valvular disease of right side of heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction, and unusual type of cyanosis (Thorson et al.), 795
Cardiac catheterization, performance of angiocardiography and, as combined procedure (Dickerson), 252
diets, gourmet cooking for, 793 (B. Rev.)
enlargement, etiology of, in coronary occlusion, hypertension, and coronary artery disease (Master), 321
failure and compensation, effect of systemic and local anoxia, of alpha-tocopherol administration, and; studies on whole blood and muscle creatine levels (Sutton et al.), 67
infarction, artificially induced, in dog, effects of cortisone and ACTH on (Hoover and Manning), 343
rate, duration of T wave and its relation to, in healthy adults (Gross), 514
vector, effect of heart position and rotation on: experimental study (Wolff et al.), 161
Cardiographic technique, 156 (B. Rev.)
Cardiology, primer of, 319 (B. Rev.)
Cardiopathies congénitales, traité des, 793 (B. Rev.)
Cardiovascular and renal hemodynamic effects of Aramine (Livesay et al.), 745
aspects of Los Angeles County mass chest x-ray survey (Jacobson et al.), 860
effects, certain, of vasopressin (Pitressin) (Wakim et al.), 77
Catheterization, cardiac, performance of angiocardiography and, as combined procedure (Dickerson), 252
Cerebral blood oxygen and carbon dioxide, effect of Parephyllin (R-3588) on (Table II) (Moyer and Snyder), 915
hemodynamic response to xanthine compound, Parephyllin (diethyl-aminoethyl theophylline hydrochloride) (Moyer and Snyder), 912

Chest wall, anterior, effect of cooling, on T wave of electrocardiogram (Rahman et al.), 394
coronary thrombosis with myocardial infarction secondary to nonpenetrating injury of (Lehmus et al.), 470
x-ray survey, mass, Los Angeles County, cardiovascular aspects of (Jacobson et al.), 860
Chinese, some epidemiologic aspects of blood pressure and its relationship to diet and constitution with particular reference to (Lowenstein), 874
Cigarette smoking, effects of, on ballistocardiograms of high school youths (Kelly et al.), 30
Circulation, extracorporeal, new method of (Juvenelle et al.), 692
time, pulmonary, elbow-left ventricle and elbow-right ventricle circulation times, obtained by means of fluorodensography with radiopaque substance (Neri et al.), 818
venous pressure, and vital capacity in patients with heart failure, effect of treatment with acetyl-digitoxin on (Table IV) (Löffler et al.), 904
visceral, 155 (B. Rev.)
Circulatory and ventilatory changes of chronic rheumatic heart disease with mitral stenosis, effect of lanatoside C on (Gray and Gray), 282
dynamics, 474 (B. Rev.)
Coarctation of aorta, presubclavian (Bahn et al.), 444
Commissurotomy, tricuspid valve, with one-year follow-up (Trace et al.), 613
Compensation, cardiac failure and, effect of systemic and local anoxia, of alpha-tocopherol administration, and; studies on whole blood and muscle creatine levels (Sutton et al.), 67
Conducting system, heart of rat with special reference to (Prakash), 241
Conduction, aberrant, in supraventricular extrasystoles eliminated by exercise (Boikan and Gunnar), 626
disturbance, atrioventricular, temporary, associated with ingestion of veratrum viride (Zumoff), 630
Congenital heart disease and acute myocardial infarction (Vesell), 604
Congestive heart failure, blood volume in, as determined with iodinated human serum albumin (Kaplan et al.), 824
effect of ganglion blocking agents in (Shuman et al.), 737
Constitution, some epidemiologic aspects of blood pressure and its relationship to diet and, with particular consideration of Chinese (Lowenstein), 874
Cor triatriatum: rare malformation of heart, probably amenable to surgery (Pedersen and Therkelsen), 676
Coronary artery disease, effect of estrogens on plasma lipids in (Oliver and Boyd), 348
"insufficiency," evaluation of term (Scherf and Golbey), 928
occlusion, acute isolated myocarditis simulating (Gillis and Walters), 117
hypertension, and coronary artery disease, etiology of cardiac enlargement in (Master), 321
thrombosis with myocardial infarction secondary to nonpenetrating injury of chest wall (Lehmus et al.), 470
Cortisone and ACTH, effects of, on artificially induced cardiac infarction in dog (Hoover and Manning), 343
therapy, risk of thromboembolic complications from (Russek et al.), 653
Creatine levels, muscle and whole blood, studies on: effect of systemic and local anoxia, of cardiac failure and compensation, and of alpha-tocopherol administration (Sutton et al.), 67
Creatinine clearance, renal plasma flow, and hematocrit, effect of continuous intravenous infusion of (Table IB) (Livesay et al.), 749
"Cyanose tardive," interventricular septal defect, pulmonary artery aneurysm with thrombosis, and paradoxical systemic arterial embolizations (Richards and Cohn), 313
Cyanosis, unusual type of, malignant carcinoid of small intestine with metastases to liver, valvular disease of right side of heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction, and (Thorson et al.), 795

D

Defibrillation, behavior during fibrillation and; extracorporeal circulation (Juvenelle et al.), 711
ventricular fibrillation and, through unopened chest, extracorporeal circulation in hypothermic dog with (Table I) (Juvenelle et al.), 696
Defibrillations, electrical; extracorporeal circulation (Juvenelle et al.), 718
Diet and constitution, some epidemiologic aspects of blood pressure and its relationship to, with particular consideration of Chinese (Lowenstein), 874
Differential vectorcardiography; dissection of vectorcardiogram (Hellerstein et al.), 887
Digitalis poisoning, bidirectional ventricular tachycardia due to (Zimdahl and Townsend), 304
Dog, effects of cortisone and ACTH on artificially induced cardiac infarction in (Hoover and Manning), 343
spread of activation in left ventricular wall of (Durrer and van der Tweel), 192

Dog's heart, normal auricular activation in (Puech et al.), 174

E

Ebstein's anomaly of tricuspid valve (Gøtzsche and Falholt), 587
disease, angiocardiographic findings in (Table IV) (Gøtzsche and Falholt), 592
catheterization findings in (Table III) (Gøtzsche and Falholt), 590
Effort, heart, artificial reduction of (Mottu), 270
Electrocardiogram, effect of cooling anterior chest wall on T wave of (Rahman et al.), 394
in hemorrhagic fever (Smyth and Powell), 218
influence of khellin (Visammin) upon electrocardiogram (Pines), 487
Electrocardiograms recorded during acute phase of hemorrhagic fever (Smyth and Powell), 234
convalescent stage of hemorrhagic fever (Smyth and Powell), 238
Electrocardiograph, direct-coupled, line-operated (Sekelj et al.), 95
Electrocardiographic abnormalities during acute phase of hemorrhagic fever, description of 27 cases with (Table I) (Smyth and Powell), 222
changes during sensitivity reaction to penicillin (Glotzer), 300
transient, identical with those of acute myocardial infarction accompanying attacks of angina pectoris (Roesler and Dressler), 520
Electrocardiography, clinical, new synthesis of some of physical foundations of (Kesselman), 360
modern, 155 (B. Rev.)
Elektrokardiogramm bei Dystrophie als Beitrag zur Physikalisch-physiologischen Analyse des Elektrokardiogramms, 154 (B. Rev.)
Electromagnetic ballistocardiograph, ballistic respiratory variation as measured by (Anderson et al.), 15
Embolizations, arterial, systemic, paradoxical, interventricular septal defect, pulmonary artery aneurysm with thrombosis, "cyanose tardive," and (Richards and Cohn), 313
Endocarditis, staphylococcus (Miller et al.), 453
Erythrocyte sedimentation rate in hemoconcentration associated with acute myocardial infarction (Volk and Losner), 658
Estrogens, effect of, on plasma lipids in coronary artery disease (Oliver and Boyd), 348
Exercise, aberrant conduction in supraventricular extrasystoles eliminated by (Boikan and Gunnar), 626
Extracorporeal circulation, new method of (Juvenelle et al.), 692
Extrasystoles, supraventricular, aberrant conduction in, eliminated by exercise (Boikan and Gunnar), 626
ventricular, significance of T-wave inversion in sinus beats following (Mann and Burchell), 504

F

Failure, heart, congestive, effect of ganglion blocking agents in (Shuman et al.), 737
effect of treatment with acetyl-digitoxin on venous pressure, circulation time, and vital capacity in patients with (Table IV) (Löffler et al.), 904
Fat tolerance in subjects with atherosclerosis: heparin effects upon lipemia, lipoproteins, and gamma globulin (Woldow et al.), 568
Fibrillation and defibrillation, behavior during; extracorporeal circulation (Juvenelle et al.), 711
during cooling and rewarming, prevention of; extracorporeal circulation (Juvenelle et al.), 721
Flarimeter, improved (Wells), 102
Floridians, native-born, and non-Floridians, rheumatic heart disease in (Saslaw et al.), 580
Fluorodensography with radiopaque substance, pulmonary circulation time, elbow-left ventricle and elbow-right ventricle circulation times, obtained by means of (Neri et al.), 818
Fonocardiografia clinica, 320 (B. Rev.)
Frontal plane ventricular gradient and its spatial counterpart, theoretical and experimental bases of (Simonson et al.), 122

G

Gamma globulin, heparin effects upon lipemia, lipoproteins, and; fat tolerance in subjects with atherosclerosis (Woldow et al.), 568
Ganglion blocking agents, effect of, in congestive heart failure (Shuman et al.), 737
Gradient, ventricular, frontal plane, and its spatial counterpart, theoretical and experimental bases of (Simonson et al.), 122

H

Heart beat, 154 (B. Rev.)
clinical disorders of, 475 (B. Rev.)
disease, congenital, and acute myocardial infarction (Vesell), 604
role of auscultation in diagnosis of (Reinhold and Nadas), 405
rheumatic, chronic, with mitral stenosis, effect of lanatoside C on circulatory and ventilatory changes of (Gray and Gray), 282
in native-born Floridians and non-Floridians (Saslaw et al.), 580
scleroderma, some aspects of (Mustakallio and Sarajas), 437

Heart beat—Cont'd
dog's, normal auricular activation in (Puech et al.), 174
effort, artificial reduction of (Mottu), 270
failure, congestive, blood volume in, as determined with iodinated human serum albumin (Kaplan et al.), 824
effect of ganglion blocking agents in (Shuman et al.), 737
of rat with special reference to conducting system (Prakash), 241
position and rotation, effect of, on cardiac vector: experimental study (Wolff et al.), 161
rare malformation of, probably amenable to surgery; cor triatriatum (Pedersen and Therkelsen), 676
valvular disease of right side of (pulmonary stenosis and tricuspid regurgitation without septal defects), malignant carcinoid of small intestine with metastases to liver, peripheral vasomotor symptoms, bronchoconstriction, and unusual type of cyanosis (Thorson et al.), 795
Hearts, congenitally malformed, autopsy diagnosis of, 793 (B. Rev.)
Hematocrit, effect of continuous intravenous infusion of Aramine on creatinine clearance, renal plasma flow, and (Table IB) (Livesay et al.), 749
Hemoconcentration associated with acute myocardial infarction, erythrocyte sedimentation rate in (Volk and Losner), 658
Hemodynamic effects, cardiovascular and renal, on Aramine (Livesay et al.), 745
response, cerebral, to xanthine compound, Parephyllin (diethyl-aminoethyl theophylline hydrochloride) (Moyer and Snyder), 912
Hemorrhagic fever, description of 27 cases with electrocardiographic abnormalities during acute phase of (Table I) (Smyth and Powell), 222
electrocardiogram in (Smyth and Powell), 218
electrocardiograms recorded during acute phase of (Smyth and Powell), 234
during convalescent stage of (Smyth and Powell), 238
Heparin effects upon lipemia, lipoproteins, and gamma globulin; fat tolerance in subjects with atherosclerosis (Woldow et al.), 568
Homogeneous torso, image surface of (Frank), 757
Hypertension, coronary occlusion, and coronary artery disease, etiology of cardiac enlargement in (Master), 321
pulmonary, studies of (Yu et al.), 330
Hypertensive diseases: causes and control, 936 (B. Rev.)
Hypertrophy, ventricular, left (Wolff et al.), 171
right, correlation of spatial vectorcardiogram with (Elek et al.), 369
Hypertrophy—Cont'd
incomplete right bundle branch block complicated by (Wolff et al.), 171

I

Image surface of homogeneous torso (Frank), 757
Infarction, cardiac, artificially induced, in dog, effects of cortisone and ACTH on (Hoover and Manning), 343
myocardial, acute, accompanying attacks of angina pectoris, transient electrocardiographic changes identical with those of (Roesler and Dressler), 520
associated with acute porphyria (Albright and Brown), 108
congenital heart disease and (Vesell), 604
erythrocyte sedimentation rate in hemoconcentration associated with (Volk and Losner), 658
prolonged survival following perforation of interventricular septum as result of (Briggs and Holt), 926
secondary to nonpenetrating injury of chest wall, coronary thrombosis with (Lehmus et al.), 470
spatial vectorcardiogram in, typified by prominent R waves in leads aV_R and V_1 (Elek et al.), 477
septal, right ventricular stenosis of Bernheim type in case of (Cordeiro), 112
Infarctions, myocardial, value of additional thoracic and abdominal unipolar leads for diagnosis of location and extension of (Lambert), 40
"Insufficiency, coronary," evaluation of term (Scherf and Golbey), 928
Integrator, electronic area (Simonson et al.), 148
Interventricular septal defect, pulmonary artery aneurysm with thrombosis, "cyanose tardive," and paradoxical systemic arterial embolizations (Richards and Cohn), 313
septum, infarcted, perforation of (Schlappi and Landale), 432
prolonged survival following perforation of, as result of myocardial infarction (Briggs and Holt), 926
Intestine, small, malignant carcinoid of, with metastases to liver, valvular disease of right side of heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction, and unusual type of cyanosis (Thorson et al.), 795
Intracardiac phonocardiography (Yamakawa et al.), 424

K

"Khellin, soluble,—Nokhel," spasmolytic action of (Barsoum and Kenawy), 297
(Visammin), influence of, upon electrocardiogram (Pines), 487

L

Lanatoside C, effect of, on circulatory and ventilatory changes of chronic rheumatic heart disease with mitral stenosis (Gray and Gray), 282

Leads aV_R and V_1, spatial vectorcardiogram in myocardial infarction typified by prominent R waves in (Elek et al.), 477

unipolar, thoracic and abdominal, additional, value of, for diagnosis of location and extension of myocardial infarction (Lambert), 40

Leistungssteigerung: Leistüng-Übermüdung-Gesunderhaltung, 935 (B. Rev.)

Lipemia, lipoproteins, and gamma globulin, heparin effects upon; fat tolerance in subjects with atherosclerosis (Woldow et al.), 568

Lipids, plasma, effect of estrogens on, in coronary artery disease (Oliver and Boyd), 348

Lipoproteins, lipemia, and gamma globulin, heparin effects upon; fat tolerance in subjects with atherosclerosis (Woldow et al.), 568

Liver, malignant carcinoid of small intestine with metastases to, valvular disease of right side of heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction, and unusual type of cyanosis (Thorson et al.), 795

Los Angeles County mass chest x-ray survey, cardiovascular aspects of (Jacobson et al.), 860

Lung biopsies, clinicopathologic correlation of, in mitral stenosis (Goyette et al.), 645

M

Medicine, modern concepts in, 155 (B. Rev.)

Metastases to liver, malignant carcinoid of small intestine with, valvular disease of right side of heart (pulmonary stenosis and tricuspid regurgitation without septal defects), peripheral vasomotor symptoms, bronchoconstriction, and unusual type of cyanosis (Thorson et al.), 795

Mitral stenosis, clinicopathologic correlation of lung biopsies in (Goyette et al.), 645

effect of lanatoside C on circulatory and ventilatory changes of chronic rheumatic heart disease with (Gray and Gray), 282

functional, produced by intra-atrial tumor (Likoff et al.), 619

summary of clinical and physiological data in 43 patients with (Table I) (Yu et al.), 334

Muscle creatine levels, studies on whole blood and: effect of systemic and local anoxia, of cardiac failure and compensation, and of alpha-tocopherol administration (Sutton et al.), 67

Myocardial infarction, acute, accompanying attacks of angina pectoris, transient electrocardiographic changes identical with those of (Roesler and Dressler), 520

associated with acute porphyria (Albright and Brown), 108

congenital heart disease and (Vesell), 604

erythrocyte sedimentation rate in hemoconcentration associated with (Volk and Losner), 658

prolonged survival following perforation of interventricular septum as result of (Briggs and Holt), 926

secondary to nonpenetrating injury of chest wall, coronary thrombosis with (Lehmus et al.), 470

spatial vectorcardiogram in, typified by prominent R waves in leads aV_R and V_1 (Elek et al.), 477

infarctions, value of additional thoracic and abdominal unipolar leads for diagnosis of location and extension of (Lambert), 40

Myocarditis isolated, acute, simulating coronary occlusion (Gillis and Walters), 117

Myocardium, atrial, smooth muscle and, distance of overlap of (Burch and Romney), 59

nature of overlap of (Burch and Romney), 61

N

"Nokhel—soluble khellin," spasmolytic action of (Barsoum and Kenawy), 297

O

Occlusion, coronary, acute isolated myocarditis simulating (Gillis and Walters), 117

hypertension, and coronary artery disease, etiology of cardiac enlargement in (Master), 321

P

Parephyllin (diethylaminoethyl theophylline hydrochloride), xanthine compound, cerebral hemodynamic response to (Moyer and Snyder), 912

(R-3588), effect of, on cerebral blood oxygen and carbon dioxide (Table II) (Moyer and Snyder), 915

Patent ductus arteriosus, atypical (Reinhold and Nadas), 419

foramen ovale, pulmonary artery thrombosis simulating pulmonic valve stenosis with (Dimond and Jones), 105

Penicillin, electrocardiographic changes during sensitivity reaction to (Glotzer), 300

Pericarditis, idiopathic, ventricular tachycardia due to, controlled by simultaneous intraveneous procaine amide and quinidine (Morris and Franklin), 919

Peripheral vasomotor symptoms, malignant carcinoid of small intestine with metastases to liver, valvular disease of right side of heart (pulmonary stenosis and tricuspid regurgitation without septal defects), bronchoconstriction, and unusual type of cyanosis (Thorson et al.), 795
Phonocardiography, intracardiac (Yamakawa et al.), 424
Pitressin, effects of intravenous administration of (Wakim et al.), 80
on systemic and pulmonic blood pressures (Wakim et al.), 81
Plasma flow, renal creatinine clearance, and hematocrit, effect of continuous intravenous infusion of Aramine on (Table IB) (Livesay et al.), 749
levels, quinidine, and rate of decline following cessation of quinidine administration, studies of (Swisher et al.), 449
lipids, effect of estrogens on, in coronary artery disease (Oliver and Boyd), 348
Poisoning, digitalis, bidirectional ventricular tachycardia due to (Zimdahl and Townsend), 304
Porphyria, acute, acute myocardial infarction associated with (Albright and Brown), 108
Pressure, blood, some epidemiologic aspects of, and its relationship to diet and constitution with particular consideration of Chinese (Lowenstein), 874
curves, "capillary," left atrial and pulmonary, during Valsalva's experiment (Björk et al.), 635
Procaine amide and quinidine, intravenous, simultaneous, ventricular tachycardia due to idiopathic pericarditis controlled by (Morris and Franklin), 919
Protractor for location of null point (Simonson et al.), 152
Pulmonary artery aneurysm with thrombosis, interventricular septal defect, "cyanose tardive," and paradoxical systemic arterial embolizations (Richards and Cohn), 313
left, absence of (McKim and Wiglesworth), 845
thrombosis simulating pulmonic valve stenosis with patent foramen ovale (Dimond and Jones), 105
"capillary" pressure curves, left atrial and, during Valsalva's experiment (Björk et al.), 635
hypertension, studies of (Yu et al.), 330
veins, functional anatomy and "throttle valve" action of (Burch and Romney), 58
nature of termination of lumina of, into left atrium (Burch and Romney), 62
nervous tissue in (Burch and Romney), 63
venous connection, total, anomaly of (Bruce and Hagen), 785
Pulse rate, behavior of blood pressure and, during experiments; extracorporeal circulation (Juvenelle et al.), 698
Pulseless disease (Jervell), 780

Q

QRS-T loop, normal (Wolff et al.), 164
Q-T interval, duration of, during anoxemia test (Roehm et al.), 204
T wave and its relation to cardiac cycle and to (Table I) (Gross), 516
Quinidine, analeptic effects of Aranthol in vasomotor depression induced by (Weisman et al.), 84
plasma levels and rate of decline following cessation of quinidine administration, studies of (Swisher et al.), 449
simultaneous intravenous procaine amide and, ventricular tachycardia due to idiopathic pericarditis controlled by (Morris and Franklin), 919

R

R waves, prominent, in leads aV_R and V_1, spatial vectorcardiogram in myocardial infarction typified by (Elek et al.), 477
Radial sheet modulator and SVEC, application of, to spatial vector ventricular gradient measurement (Simonson et al.), 144
Radiopaque substance, pulmonary circulation time, elbow-left ventricle and elbow-right ventricle circulation times, obtained by means of fluorodensography with (Neri et al.), 818
Rat, heart of, with special reference to conducting system (Prakash), 241
Regurgitation, aortic, predominant lesion: clinical data (Table IB), (Goldberg et al.), 532
physiologic data (Table IIB) (Goldberg et al.), 548
Renal and cardiovascular, hemodynamic effects of Aramine (Livesay et al.), 745
Respiratory variation, ballistic, as measured by electromagnetic ballistocardiograph (Anderson et al.), 15
Rheumatic heart disease, chronic, with mitral stenosis, effect of lanatoside C on circulatory and ventilatory changes of (Gray and Gray), 282
in native-born Floridians and non-Floridians (Saslaw et al.), 580

S

Scleroderma heart disease, some aspects of (Mustakallio and Sarajas), 437
Sedimentation rate, erythrocyte, in hemoconcentration associated with acute myocardial infarction (Volk and Losner), 658
Septal defect, atrial (Reinhold and Nadas), 415
interventricular, pulmonary artery aneurysm with thrombosis, "cyanose tardive," and paradoxical systemic arterial embolizations (Richards and Cohn), 313
ventricular, and single ventricle (Reinhold and Nadas), 413
infarction, right ventricular stenosis of Bernheim type in case of (Cordeiro), 112

Septum, interventricular, infarcted, perforation of (Schlappi and Landale), 432
prolonged survival following perforation of, as result of myocardial infarction (Briggs and Holt), 926
Serum albumin, human, iodinated, blood volume in congestive heart failure as determined with (Kaplan et al.), 824
Shutter, asymmetrical, ballistoscope recording with aid of (Losner), 34
description of (Losner), 35
Sinus beats, significance of T-wave inversion in, following ventricular extrasystoles (Mann and Burchell), 504
Smoking, cigarette, effects of, on ballistocardiograms of high school youths (Kelly et al.), 30
Spasmolytic action of "soluble khellin—Nokhel" (Barsoum and Kenawy), 297
Spatial counterpart, theoretical and experimental bases of frontal plane ventricular gradient and (Simonson et al.), 122
vectorcardiogram, correlation of, with right ventricular hypertrophy (Elek et al.), 369
in myocardial infarction typified by prominent R waves in leads aV_R and V_1 (Elek et al.), 477
ventricular gradient (Simonson et al.), 134
Staphylococcus endocarditis (Miller et al.), 453
Stenosis, aortic (Reinhold and Nadas), 408
ballistocardiogram in (van Lingen et al.), 560
predominant lesion: clinical data (Table IA) (Goldberg et al.), 528
physiological data (Table IIA) (Goldberg et al.), 536
"isolated" pulmonary valvular (Reinhold and Nadas), 410
mitral, clinicopathologic correlation of lung biopsies in (Goyette et al.), 645
effect of lanatoside C on circulatory and ventilatory changes of chronic rheumatic heart disease with (Gray and Gray), 282
functional, produced by intra-atrial tumor (Likoff et al.), 619
pulmonic valve, with patent foramen ovale, pulmonary artery thrombosis simulating (Dimond and Jones), 105
ventricular, right, of Bernheim type in case of septal infarction (Cordeiro), 112
Stromungsgesetz, das, des Blutkreislaufes, 634 (B. Rev.)

T

T wave, correlation between height and duration of (Gross), 517
duration of, and its relation to cardiac rate in healthy adults (Gross), 514
inversion, significance of, in sinus beats following ventricular extrasystoles (Mann and Burchell), 504
of electrocardiogram, effect of cooling anterior chest wall on (Rahman et al.), 394
Tachycardia, ventricular, bidirectional, due to digitalis poisoning (Zimdahl and Townsend), 304
Tachycardia—Cont'd
due to idiopathic pericarditis controlled by simultaneous intravenous procaine amide and quinidine (Morris and Franklin), 919
paroxysmal, Wolff-Parkinson-White syndrome associated with (Dunn et al.), 462
Tetralogy of Fallot (Reinhold and Nadas), 416
Thoracic and abdominal unipolar leads, additional value of, for diagnosis of location and extension of myocardial infarctions (Lambert), 40
Thromboembolic complications from cortisone therapy (Russek et al.), 653
Thrombosis, coronary, with myocardial infarction secondary to nonpenetrating injury of chest wall (Lehmus et al.), 470
pathogeneses and treatment of, 319 (B. Rev.)
pulmonary artery aneurysm with, interventricular septal defect, "cyanose tardive," and paradoxical systemic arterial embolizations (Richards and Cohn), 313
simulating pulmonic valve stenosis with patent foramen ovale (Dimond and Jones), 105
"Throttle valve" action, functional anatomy and, of pulmonary veins (Burch and Romney), 58
Torso, homogeneous, image surface of (Frank), 757
Tricuspid valve commissurotomy with one-year follow-up (Trace et al.), 613
Ebstein's anomaly of (Gøtzsche and Falholt), 587
Tumor, intra-atrial, functional mitral stenosis produced by (Likoff et al.), 619

U

Unipolar leads, additional thoracic and abdominal, value of, for diagnosis of location and extension of myocardial infarctions (Lambert), 40

V

Valsalva's experiment, left atrial and pulmonary "capillary" pressure curves during (Björk et al.), 635
Valve, aortic, bicuspid, clinical diagnosis of (Tranchesi et al.), 664
tricuspid, commissurotomy with one-year follow-up (Trace et al.), 613
Ebstein's anomaly of (Gøtzsche and Falholt), 587
Valvular disease, aortic, correlation of clinical and physiologic findings in patients with (Goldberg et al.), 555
dynamics of (Goldberg et al.), 527
of right side of heart (pulmonary stenosis and tricuspid regurgitation without septal defects), malignant carcinoid of small intestine with metastases to liver, peripheral vasomotor symptoms, bronchoconstriction, and unusual type of cyanosis (Thorson et al.), 795

Vasomotor depression induced by quinidine, analeptic effects of Aranthol in (Weisman et al.), 84
symptoms, peripheral, malignant carcinoid of small intestine with metastases to liver, valvular disease of right side of heart (pulmonary stenosis and tricuspid regurgitation without septal defects), bronchoconstriction, and unusual type of cyanosis (Thorson et al.), 795
Vasopressin (Pitressin), certain cardiovascular effects of (Wakim et al.), 77
Vector, cardiac, effect of heart position and rotation on: experimental study (Wolff et al.), 161
Vectorcardiogram, dissection of: differential vectorcardiography (Hellerstein et al.), 887
spatial, correlation of, with right ventricular hypertrophy (Elek et al.), 369
in myocardial infarction typified by prominent R waves in leads aV_R and V_1 (Elek et al.), 477
Vectorcardiography, differential; dissection of vectorcardiogram (Hellerstein et al.), 887
Veins, pulmonary, functional anatomy and "throttle valve" action of (Burch and Romney), 58
Venous connection, pulmonary, total, anomaly of (Bruce and Hagen), 785
pressure, circulation time, and vital capacity in patients with heart failure, effect of treatment with acetyl-digitoxin on (Table IV) (Löffler et al.), 904
Ventilatory changes, circulatory and, of chronic rheumatic heart disease with mitral stenosis, effect of lanatoside C on (Gray and Gray), 282
Ventricle, elbow-left, and elbow-right ventricle circulation times, pulmonary circulation time, obtained by means of fluorodensography with radiopaque substance (Neri et al.), 818
left, investigation of activation conditions at epicardial surface of (Durrer and van der Tweel), 193
with bundle branch block, depolarization of (Kennamer and Prinzmetal), 769
Ventricular extrasystoles, significance of T-wave inversion in sinus beats following (Mann and Burchell), 504
fibrillation and defibrillation through unopened chest, extracorporeal circulation in hypothermic dog with (Table I) (Juvenelle et al.), 696
gradient, frontal plane, and its spatial counterpart, theoretical and experimental bases of (Simonson et al.), 122
measurement, spatial vector, application of radial sheet modulator and SVEC to (Simonson et al.), 144
hypertrophy, right, correlation of spatial vectorcardiogram with (Elek et al.), 369
stenosis, right, of Bernheim type in case of septal infarction (Cordeiro), 112
tachycardia, bidirectional, due to digitalis poisoning (Zimdahl and Townsend), 304
due to idiopathic pericarditis controlled by simultaneous intravenous procaine amide and quinidine (Morris and Franklin), 919
paroxysmal, Wolff-Parkinson-White syndrome associated with (Dunn et al.), 462
wall, left, of dog, spread of activation in (Durrer and van der Tweel), 192
Veratrum viride, temporary atrioventricular conduction disturbance associated with ingestion of (Zumoff), 630
Visceral circulation, 155 (B. Rev.)

W

Wolff-Parkinson-White syndrome associated with paroxysmal ventricular tachycardia (Dunn et al.), 462

X

Xanthine compound, Parephyllin (diethylaminoethyl theophylline hydrochloride), cerebral hemodynamic response to (Moyer and Snyder), 912
X-ray survey, chest, mass, Los Angeles County, cardiovascular aspects of (Jacobson et al.), 860

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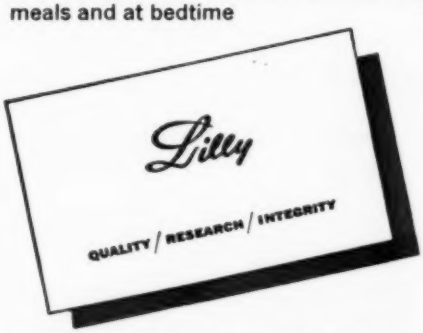

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